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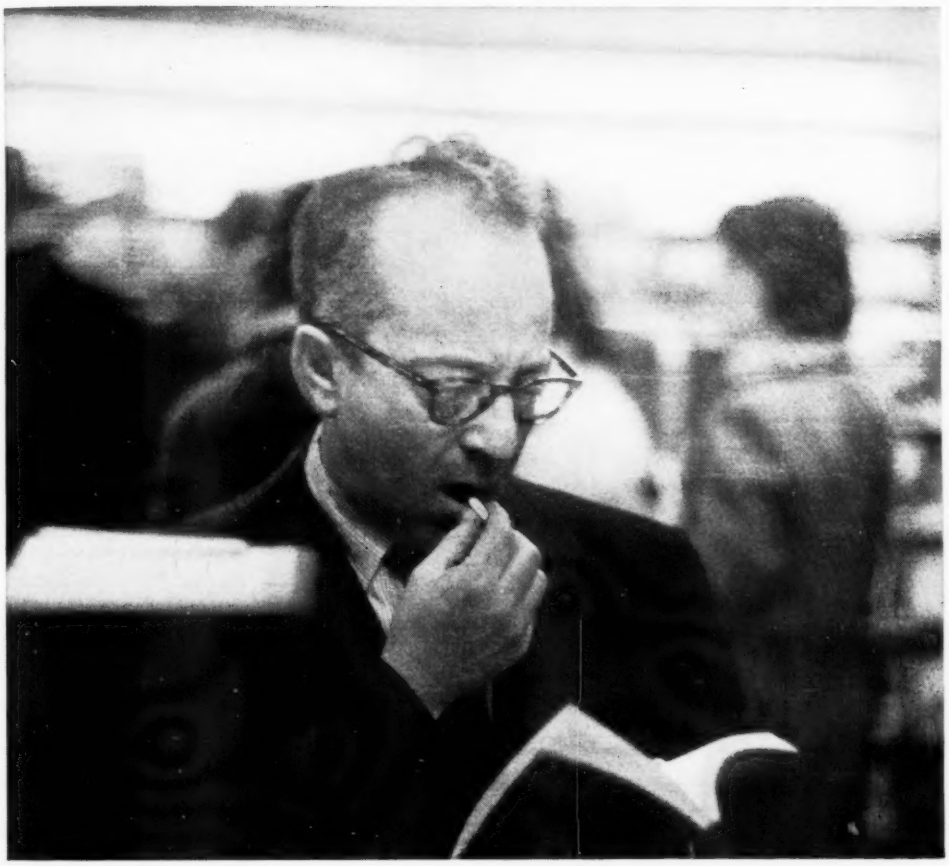

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PLAN NOW TO ATTEND

The 41st Annual International Scientific Assembly

of the

Interstate Postgraduate Medical Association
of North America

• • •

Cleveland, Ohio, October 22, 23, 24 and 25, 1956

A New Method of Treating Emotionally Induced Illness Adaptable to General Practice

JOHN A. SCHINDLER*

The Monroe Clinic, Monroe, Wisconsin

THE greatest problem in medicine today is the development of a better treatment for functional or emotionally induced illness. At least half the patients seen in doctors' offices are there primarily because they have functional illness. That is the first reason we need a good treatment.

The second reason, which is even more important, is that the treatment we give patients with emotionally induced illness generally is by far the worst treatment we give to any group, excluding possibly only those who have one of the neuroscleroses, for which there is no treatment. In fact, it generally is no better than, and in principle actually is the same as, the type of treatment the witch doctors practiced in primitive times. I will enlarge on that later in this discussion.

*Department of Internal Medicine, The Monroe Clinic, Monroe, Wisconsin.

Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

Thirdly, doctors as well as patients need a better treatment for emotionally induced illness, because this is the disease that frazzles our own nerves—that destroys that quality in doctors which Osler said was so important, their equanimity.

You probably all know the story of the doctor who had had a very hard day. He had been seeing psychosomatic patients all day, and by 6 o'clock was about ready to crawl out of his office. As he started out he saw one more patient in the waiting room, a little old lady. He thought, "This ought to be easy," so he called her in. As she came into the office she said, brushing herself violently, "Doctor, you *must* help me, I can't keep these butterflies off me." He looked at her a moment, started brushing himself, and said, "Please, lady, don't brush them off on me."

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Fourthly, the profession as a profession needs a better treatment for emotionally induced illness. If one takes the trouble to in-

vestigate those persons who publicly criticize the medical profession, one almost invariably finds that they themselves or some member of their family has had a prolonged emotionally induced illness, over the management of which many misapprehensions and a good deal of rancor have developed.

Also, if the quacks and cultists had to exist on organic disease, for which they have no treatment, they would not last three weeks; they can exist solely because our treatment for emotionally induced illness is so ineffective. Actually, their method of treating it is based on the same principle as that which we usually use, and in many respects it is better.

Let us review briefly the treatment we generally give patients with emotionally induced illness. About 85 per cent receive what we can call "substitution therapy." Substitution therapy was the treatment used by the witch doctor in primitive times. It consists of giving the patient an explanation for his disease which is not the proper explanation but is something the patient can understand and is easy for the doctor to give. The witch doctor told his patient, "You are possessed of evil spirits." Then he proceeded very effectively and dramatically to drive out those evil spirits. I wish sometimes I could use his methods; I wish sometimes I could put on his mask and use his rattles—I believe I could scare not only the devil but the illness out of some of the tough patients I see. Of course the witch doctor did have some success with this therapy or he could not have stayed in practice.

Later on, the medieval doctor gave his patient the substitution diagnosis. One of his four humors was out of balance—and it was always the blood, because that was the only one that could be removed easily. This doctor actually did not have a thing for treating organic disease, but he, too, had considerable success with his substitution treatment or he would not have stayed in practice.

The modern cultist gives his patient the substitution diagnosis; he tells him he has a vertebra out of place and then proceeds to put it back into place. He, too, has some success.

Substitution therapy is successful for this reason: Regardless of the type of substitution, as long as it is given with a serious air of professional competence it will help 60 per cent of the patients for a period of two months—and that is long enough for advertising.

The modern physician uses such substitution diagnoses as anemia, which explains weakness, tiredness, dizziness and many other things; a high or low metabolic rate; a high or low blood pressure—or a high or low something else. Out in the country a good one is a sluggish liver—you never get into trouble with that. If one is not careful with substitution diagnoses, one will give the patient an iatrogenic illness. Any diagnosis that might lead to surgery is not a good one. If you tell a woman that the pain in her lower abdomen is due to an ovary, sooner or later that ovary will be removed—if not by you, by someone else. After that it will be the other ovary, and then you will have a patient who *really* has a psychosomatic illness—and you, doctor, will *really* lose your equanimity.

Of course, substitution therapy would be impossible without what we call "the art of medicine." A wag in Philadelphia recently said that the art of medicine is that part of medicine which is almost wholly confined to the problem of keeping the psychosomatic patient from going to another doctor. Think that over and see if it isn't true.

Another method of treating psychosomatic illness is what we might call "nerves plus sedatives." Trying to be more honest, the doctor tells the patient, "There is nothing wrong with you, it's just your nerves," and then prescribes some form of sedative. Only 7 per cent of the functional patients in this country are treated by that method, because it is less than a tenth as effective as substitution therapy. If every doctor the patient consulted would tell him the same thing, it would work, but always someone along the line is going to give him an organic diagnosis.

Another possible method of treating emotionally induced illness would be what is known as "adequate traditional psychotherapy." However, we may as well face this problem realistically; irrespective of the effectiveness of this type of therapy, it is impossible, *merely on the basis of time*, to treat the aver-

age psychosomatic patient by this means. If one does it in less than the required 15 to 20 hours, it is not done properly; you are, again, not doing a good job. With this method, a doctor could treat the equivalent of one patient a day—by working 20 hours a day. The average doctor in the United States sees 23 patients a day, 12 of these primarily because of emotionally induced illness.

In this state of affairs, anyone casting around for some new form of treatment, as we have tried to do, can, I believe, be excused; even their (our) ineptness can be excused.

We have resorted to machinery in treating emotionally induced illness—yes, machinery. We have tried to utilize some of the wonderful modern inventions for communicating ideas from one person to another. After all, that is primarily what the psychosomatic patient needs—some new ideas as to why he is sick, and then how he can finish the rest of his life without getting that disease. We use tape recorders connected automatically to a slide projector, and the patient spends 15 to 20 hours watching and listening to such audio-visual presentations.

Before I discuss that point further, however, I want to say that the physician first must sell himself to the patient. There are two ways of doing this. First, let him know that you and your entire office staff have his interest at heart as a human being; always make sure he leaves your office feeling that at last he has met someone with the warmth of human kindness. Second, give that patient the most thorough, the most meticulously careful examination he has ever had. If you don't, after the examination he will prefer to believe the doctor who gave him an organic explanation and a better examination. Your examination must be the one to end all further examinations. You should close every possible avenue of ill health toward which that patient's mind is apt to go, and you can do that only by knowing what fears regarding his ill health are in his mind. A careful history tells you what these fears are; this takes the inexpert about an hour and the expert only about 20 minutes.

We also give patients one of the Cornell medical indexes to fill out. It contains 195 questions, arranged in such a way that a glance at the answers tells you what fears the patient has in regard to his health; you learn at once what avenues you must close. For instance, if he has had some bleeding from the rectum, unless you do a colon x-ray and use a sigmoidoscope, after you have started therapy he will stop you and say, "But Doctor, I still am having that blood from my rectum." Then you either have to give him some weak assurance or you have to backtrack, admitting that, after all, you didn't know all about him.

After the examination and after the last test, the patient comes back into my office and I review quite briefly all the tests he has had: "This test was so-and-so, it was normal; your x-ray of so-and-so was normal, your physical examination was so-and-so and that is all normal. In other words, your body is in excellent physical condition, but your trouble is that the parts aren't functioning right." We begin by calling the disease "functional disease": "You are like a railroad in which the track and the rolling stock and everything else are in perfect condition but the dispatcher isn't doing his work properly, and he can get that railroad all balled up. That is what is happening to your body. Tomorrow morning we want you and your wife (or husband) to come in and we will show you how your functional disease works. Any questions you may have will be answered then." And that is all there is to that interview.

The next morning the patient and his or her spouse come to the clinic (this can be the general practitioner's office as well) and the nurse takes them to a comfortable room and starts the audio-visual presentation, which runs entirely automatically. We like to have the patient and his or her spouse alone. Occasionally when the patient load is heavy we may have two couples together, but we like to have only one couple because one can say to the other, "See, that is you! Look at that, that's you!" They are not likely to talk to each other that way when other people are in the room.

The first morning they spend three hours during which we explain functional disease to them. First we tell them that it is very common—and I always tell them that I myself

have a functional disease, and I have. I tell them that the husband (or wife) will have one next—that everyone has them, that it is no disgrace. The explanations we give are not the symbolic ones so often used. For instance, to tell a patient that he has a lump in his throat because there are things in his life that he cannot swallow is very ineffective; it does not convince him. Some time ago I saw a patient who had been told that he had diarrhea because he didn't like his mother-in-law and his diarrhea was his organ language for trying to get rid of her. That type of explanation not only is ineffective, it isn't correct. We know today how functional disease works, and can use the physiologic explanations we have. These have been given us by Lange, James, Canon, Wolf, Hans Selye, Dunbar, Alschule and many others; we have much material for explaining the different phases of functional disease.

We explain first what an emotion is. An emotion is a physical thing. Once a patient understands that, the rest falls into line. We use the definition of Lange and James, that an emotion is a state of mind that manifests itself by physical changes in the body, and the physical changes *are* the emotions. Then as an example of a common emotion we use anger. which Dr. Canon of Harvard studied in great detail. We show the patient that the internal changes are just as characteristic for that emotion as the external (facial) ones. We stress particularly the following changes. When a person is angry his blood pressure rises. We have measured rises of from 130 to 340 systolic, and when that happens a blood vessel can, and frequently does, break in the brain, resulting in instant death or paralysis. The patient understands this, and often he will say, "My gosh, one can die of an emotion"—and one can. Even more effective is the fact that in a fit of anger the coronary arteries squeeze down, and if one has angina pectoris or is over 50 years old (in both of which cases there is narrowing of the arteries) a bout of anger can cause an acute coronary occlusion. Then we use the example of John Hunter, who had a bad temper and angina pectoris; he always said, "The first rascal who gets me angry will kill me." As you will recall, it remained for a medical meeting which Hunter was attending to make him angry enough to produce the bout of anger which finally gave him his fatal coronary occlusion.

Then we present examples of 40 of the more common syndromes we see in emotionally induced illness. We always start with the life situation, how a person reacts to something, and then illustrate the physiology which produces the final illness. Many of our slides are cartoons or diagrams.

At the end of the three hour session, the patient and his or her spouse come back into the office, and almost invariably they say, "Doctor, you were talking about me all morning. Why didn't someone tell me this before?" And they are very grateful.

We convince over 95 per cent of these patients that what they have is functional disease (there are a few who are recalcitrant). That is the most important single step. In fact, in many instances once you have shown a patient that he has a functional illness, that is all you need to do. It is best to add this further advice: that they will perhaps keep having these emotions that are giving them the symptoms and will have to learn to live with them. At least they will not have to worry about them, since they know what they are. I always use myself, again, as an example; I have a psychosomatic illness which I get from my practice. I have also cited examples of other doctors who have such disorders, and when the patient hears this he isn't as concerned about it as he was.

If you did only this, you would be doing many people a great deal of good.

During the next 12 to 15 hours we try to show patients how they can get over their emotional stress. They come back at weekly intervals for an hour or two of further audiovisual presentation.

We boil down emotional stress to two common denominators. First, emotional stress stems from some basic psychologic needs, such as for security, attention, creativeness, self-esteem and so on, which are not being satisfied. Again we use examples of people and pictures of people reacting to situations—how an emotionally induced illness is being pro-

duced. As they watch, they can pick out the parts that apply to their own situations. Usually they get a better idea of psychologic needs from this audio-visual presentation than the average student of psychology does in college.

The other common denominator for emotional stress is the fact that it develops because the person is trying to meet adult situations with childish technics. Here we go through the various immaturities, and again we assure the patient that everyone has some very glaring immaturities, because in our society today we are not teaching people to become mature. It is something one has to learn, and because there has been no place to learn it we all have glaring immaturities in some department or other of our personalities. Even executives of large corporations have them. That approach negates any defensive mechanism in regard to that.

Then we show them about 14 different types of immaturities, always starting with an example of an actual patient and his reaction to a situation and carrying through to an emotionally induced illness. Again the listener picks out the things that apply to his own situation. Here the spouse comes in handy; he or she says, "That's you, that's the way you act."

After these six to eight hours of learning the common denominators underlying emotional stress the patient usually can tell me what is causing his trouble. Often he will relate incidents which he did not tell me during the initial interview.

Finally, we try to present practical ways for meeting the ordinary immaturities and to fill the lack of basic psychologic needs. This again we put into very practical terms, always using actual illustrations. For instance, the patient who is immature in that he cannot change the emotion of a given situation is like a child. Watch children; you give them a sack of candy and they laugh; tell them they cannot go outdoors and they cry. Their emotions are the mirror image of their situation. An adult with that immaturity is anxious and apprehensive all the time, because almost every adult life situation has an element of anxiety or apprehension; he does not know how to handle such elements, and in this respect he is a child.

We use a practical trick for handling such an immaturity. We say, "All right, you are guilty of this, you are in the habit of doing this, but how are you going to handle it? Watch yourself, and when you think a situation is arising that will irritate you and upset you, make a little sign like this (circle of thumb and forefinger), silly as it may sound, and say, 'Nuts! I'm not going to let this irritate me,' and with practice you will become very adept at it; then a terrific situation can come along and you very pleasantly can make your sign and say, 'Nuts!' "

The entire series takes 14 to 20 hours. We have different series for different patients, depending on their particular lack. For instance, we have an hour on sexual difficulties, which we do not show to all patients because it is quite an intimate hour.

It is difficult to evaluate the effectiveness of any treatment of the psychosomatic patient. Psychiatrists, too, as well as anyone else, have to count on "substitution" improvement. *Any* form of treatment, as I said, will improve the patient for two months. Will the improvement continue longer than that? We use the following criteria to evaluate the effectiveness of treatment: If a patient does not have to go back to a doctor for a year, and if at the end of a year he says he has been well, we score his improvement as 4 plus. If he does not consult a physician for a year but at the end of the year says, "I still have this thing but I don't worry about it," we consider it a 2 plus improvement. If he goes to doctors all year long and still has his old symptoms, and possibly new ones, he is unimproved. Even on the basis of such criteria it is easy to get wrong figures, and I hesitate to give you ours because they sound too good—they sound so good that I myself am quite sure they cannot be correct.

The results of treatment of emotionally induced illness by the various methods are very interesting. The same doctor treated a series of patients by the substitution method, by the "nerves-sedative" method, by some method of psychiatry, and also by the method outlined herein. Some 258 patients were treated by the substitution technic; only 8 per cent were 4

plus improved, 65 per cent were unimproved, and the remainder were classed as 2 plus improved. These results were quite reversed by the type of treatment I have outlined: 65 per cent of our patients are 4 plus improved and about 10 per cent unimproved.

The unimproved patients constitute a particularly difficult class. These are the patients we usually refer to a psychiatrist if we refer them at all. Actually, less than 1 per cent of all persons with psychosomatic illness in this country are referred to psychiatrists. These patients do not get along under any form of treatment; they have personality difficulties such as compulsions or obsessions and cannot be treated successfully by any method. However, the ordinary psychosomatic patients—the 85 per cent—have emotional stress either because of their life situations or because they do not know how to manage ordinary situations. For this class of patients our treatment is very effective.

We do not have either the tape recordings or the slides available for distribution, but I believe any physician who uses this method should make the recordings in his own voice. This adds a great deal to the effectiveness of the treatment. The slides can easily be duplicated, and we will be glad to duplicate them for you.

We also give patients a book which I wrote. "Manual for Functional Patients" was its original title, but the publisher, thinking it might have a public appeal, changed it to "How to Live 365 Days a Year." The book contains everything we tell our patients, in about the same order we tell it and with all the stories that we use.

I believe we can improve our presentation greatly. Treatment of functional disease is in its infancy, and I am sure that in the future some such method will have to be used to give these patients the treatment they deserve. I cannot see any other way it can be done.

41st Annual

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Cleveland, Ohio, October 22-25, 1956

Hyperventilation Syndromes: Clinical and Physiologic Observations

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Radioactive Iodine in the Treatment of Thyroid Disease

JOHN Z. BOWERS*

University of Wisconsin Medical School, Madison

JOHN Z. BOWERS

RADIOACTIVE iodine has held an important role in the diagnosis and treatment of thyroid disease. Determination of the uptake of radioactive iodine by the thyroid gland is a reliable laboratory diagnostic procedure. Primary hyperthyroidism may be treated effectively with radioactive iodine. Its use in thyroid carcinoma is in general limited to patients with metastatic tumors which histologically are well differentiated.

Radioactive iodine as used clinically (I^{131}) is obtained as a by-product from the fission of uranium or by bombardment of tellurium. It is available from the United States Atomic Energy Commission to authorized laboratories equipped to handle radioactive elements. Knowledge of the basic principles for safe handling and measurement of radioisotopes is prerequisite to obtaining these materials.

Like all radioactive elements, radioiodine emits radioactivity over a specific period. The amounts emitted toward the end of this period are quite small; the greater part is emitted during the first half of the total period, and thus one commonly refers to the half-life of the element. Radioactive iodine (I^{131}) has a half-life of eight days.

Clinical use of radioactive iodine is based on three physicochemical characteristics of the material: (1) It has the same chemical and biochemical properties as stable iodine, so that it is trapped avidly by the thyroid gland and launched through its metabolic pathway; (2) it emits beta rays which are destructive to tissue; (3) it also emits gamma rays which are highly penetrating and can be detected over the site of concentration.

The thyroid gland traps iodine with an avidity directly proportional to the level of thyroid function. In a tracer study for diagnosis one uses small amounts of radioiodine which are incapable of damaging tissue but which reflect accurately the level of thyroid function. In therapy one gives amounts several hundred times larger in order to destroy appropriate amounts of the gland.

Diagnosis of Thyroid Disease

A radioactive iodine tracer study is a valuable and reliable procedure for determining

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

the level of thyroid function, particularly in instances of hyperfunction. The procedure is simple. The patient drinks the material in a small glass of water, and the percentage of the administered dose concentrated in the gland is determined at one or more intervals. Frequently a single measurement at the end of 24 hours is made; urinary measurements have been almost universally discarded. Generally, a concentration greater than 40 per cent of the administered dose is considered evidence of increased thyroid function, while less than 15 per cent indicates hypothyroidism.

Extraneous factors—Too often, patients are referred for studies with radioactive iodine while under a program of therapy which makes a reliable test impossible. Those antithyroid drugs which have goitrogenic properties and interfere with the metabolic pathway of iodine give a distorted result which does not truly represent the level of thyroid function. Patients should not have received propylthiouracil, methimazole (TAPAZOLE®), iothiouracil (ITRUMIL®), thiocyanate or similar compounds for one week before the radioiodine test.

A thyroid gland saturated with iodine is incapable of trapping iodine from the blood. Thus, patients under therapy with iodine likewise should not receive such medication for one week before the test. Some expectorants, gallbladder visualization dye and LIPIODOL® also contain iodine. Whenever a test result contradicts what seems to be an obvious clinical impression, one should determine whether or not the patient has consumed these materials recently.

With the development of the radioactive iodine uptake study as a reliable procedure for determining the level of thyroid function, physicians now have three laboratory methods to fortify their clinical impressions in thyroid problems, thus facilitating the sorting out of the neurocirculatory asthenic patients with tremor, weight loss, palpitation and fatigability, or overweight patients who complain of sluggishness, constipation and sensitivity to cold.

The basal metabolic rate remains the most generally available laboratory test for thyroid function. Perhaps because of its availability, too much credence frequently is placed in it, for often the procedure is carried out when conditions are not truly "basal." The range of the normal basal metabolic rate is generally plus 20 per cent to minus 20 per cent, and figures within this range are *normal.* The first determination in an apprehensive patient usually is elevated, but as the person becomes familiar with the machine and the technician a reliable reading will be obtained. A sedative may be desirable for patients who are obviously apprehensive.

The determination of the protein-bound iodine of the blood is often used in studying thyroid function. This test is best done in the rather few laboratories where it is performed routinely, for inadvertent contamination with iodine must be scrupulously avoided. Patients who recently have received iodine or iodine-containing compounds will show elevated levels not truly indicative of thyroid function.

Serum cholesterol levels have been examined in various thyroid diseases. They may be quite helpful in determining hypofunction but have little value in hyperfunction. Serial determinations frequently may be necessary, and at times a short course of thyroid U.S.P. or a single dose of TSH may bring out a high level which has diagnostic value.[1]

Radioiodine has been helpful at times in locating hyperfunctioning benign or malignant thyroid tissue in extrathyroidal locations. Further, patients who are hypermetabolic because of self-administered thyroid will have normal or depressed radioiodine uptake in association with an elevated basal metabolic rate.

Treatment of Thyroid Disease With Radioactive Iodine

Radioactive iodine has been used in the treatment of hyperthyroidism since 1941[2] and is now well established as a reliable therapeutic agent. In general it is used in treating primary hyperthyroidism. It should not be given to patients with nodular goiter, for dose estimation is difficult, rather large amounts of material are required and there is the possibility of missing a malignancy. However, in primary hyperthyroidism the therapeutic results have been quite satisfactory.

Radioactive iodine therapy for hyperthyroidism is an example of a procedure which at first was used only in selected cases but with time has become increasingly popular. Thus it has been restricted by some to patients who were considered poor candidates for subtotal thyroidectomy. Patients who have had previous thyroid surgery, cardiovascular disease or comparable conditions have received radioiodine. There is considerable enthusiasm for its use in treating hyperthyroidism complicated by exophthalmos, particularly when the exophthalmos is progressive or associated with periocular edema, conjunctivitis or ophthalmoplegia. The frequency of postoperative progression in these cases is well known.

Many clinics have restricted the use of radioiodine to patients over 45 years of age because of the fear of delayed malignancy in thyroid remnants or perithyroidal tissues. The fact that we have patients who received radioactive therapy whom we have followed for more than 10 years without evidence of malignancy suggests that these apprehensions may not be valid.

There are, of course, similar apprehensions about genetic changes as a result of the whole body irradiation which occurs before the radioiodine is concentrated in the thyroid gland. Opinions differ considerably as to the amount of irradiation required to produce a significant genetic event such as doubling the spontaneous mutation rate. A great deal more information is needed about radiation genetics before final answers can be given.[3]

Therapeutic use of radioiodine in hyperthyroidism is a simple procedure. Following a determination of the percentage uptake of a tracer dose of radioiodine, a therapeutic dose is administered based on a dose of 75 microcuries of radioactive iodine per estimated gram of thyroid weight. The latter poses the only difficulty in determining the dose of radioiodine. Estimating the thyroid weight by means of palpation carries on obvious degree of error.

There seems to be a growing feeling that one or more small doses of radioiodine are preferable to a single large dose—thus, 75 microcuries per gram as compared with 100 or 125 microcuries per gram. The use of smaller repeated doses sharply reduces one sometimes troublesome problem, the development of hypothyroidism. Occasionally a patient will lose scalp hair, but this, fortunately, always reappears.

It is now agreed that special precautions against radiation exposure are unnecessary with the doses used in treating primary hyperthyroidism. The patients remain completely ambulatory and carry on their usual activities.

In treating thyroid carcinoma, use of radioiodine has waned in popularity—or perhaps has fallen into its proper position. When the malignancy is restricted to the neck the treatment is primarily surgical. Radioiodine generally is reserved for situations where there are distant, surgically inaccessible metastases. Further, the use of radioiodine is, under metabolic reservations, for only those tumors which show acinar differentiation; i.e., malignant adenoma, papillary adenocarcinoma, and adenocarcinoma may concentrate adequate amounts of the material. In cases of these tumors there have been numerous instances of striking beneficial results with radioiodine. Side effects such as bone marrow depression may be a problem here because of the size of dose required.

Summary

A radioiodine uptake study is a simple, reliable procedure for establishing the level of thyroid function, particularly for differentiating euthyroidism from hyperthyroidism. Further, radioactive iodine has an important place in the treatment of primary hyperthyroidism. Its use in treatment of thyroid cancer should be limited to patients with metastatic disease and in general is possible only in cases of malignant adenoma, papillary adenocarcinoma, and adenocarcinoma.

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The Diagnostic Problem of Histoplasmosis

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HISTOPLASMOSIS is not another of those rare diseases that catch the imagination because of their poetic names. It is significantly common in the East Central portion of the United States and thus may challenge many an astute diagnostician to discover it in one or all of its clinical variations. As a disease entity it is primarily granulomatous in nature, mimicking particularly tuberculosis in its pulmonary form. The etiologic agent is the fungus *Histoplasma capsulatum*, an organism highly invasive to the reticulo-endothelial system. Experimental and epidemiologic evidence greatly favors the respiratory tract as the portal of entry for the fungus. Thus, the respiratory tract is most often involved, although the disease may or may not cause pulmonary infiltration.

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History

A brief historical account will serve to emphasize our intellectual lag in diagnostic acumen concerning this fungal disease. Its first description as a disease proper was furnished by Darling[1,2] in 1905 in Panama. He both discovered and named the organism *H. capsulatum*, though he was unaware of its true nature. Rocha-Lima[3] classified the organism as a fungus in 1912, but it was first cultured successfully some 21 years later by deMonbreun[4] from an infant succumbing to histoplasmosis.

As originally considered, histoplasmosis had a rather exotic character, being fatal in all instances. In fact, it seemed to be foreign to this country until in 1926 the first case was reported from Minnesota.[5] A review of the literature on the subject was published in 1945, and in the 40 years since its discovery only 71 cases had been recorded throughout

the world.[6] An interpretation of this last statement on the basis of our present knowledge could only signify that many misdiagnoses and missed diagnoses were responsible for so few cases being reported.

Great strides in the recognition of the prevalence of histoplasmosis as a predominantly benign disease that is only rarely fatal have come within the past decade. Accurate detection of the disease and its epidemiologic scope were facilitated by the development of diagnostic antigens, serologic procedures, skin testing and mouse isolation technics.

Epidemiology

To emphasize more fully that the physician and surgeon will often be faced with the disease histoplasmosis, whether they diagnose it properly or not, its endemism is briefly considered. Histoplasmin skin sensitivity is highly prevalent among persons living in the East Central States or Lower Mississippi Basin (positive in 45 to 90 per cent), and we must therefore assume that infection with *H. capsulatum* is ever-present in that area. In direct accord, the area of highest incidence of pulmonary calcifications, in many of which cases the patients do not react to tuberculin, can be practically superimposed on this same area composed of the Lower Mississippi Basin States. These calcified, healed pulmonary lesions and positive histoplasmin skin sensitivities both result from infection with the *Histoplasma* fungus. Many a fever of undetermined origin in the Midwest could represent another case of benign histoplasmosis, undiagnosed.

Twenty-one epidemic outbreaks of histoplasmosis involving a total of 182 persons have been described in the literature to date.[7-9] The great majority of these epidemics were concentrated within the areas having a high or moderately high incidence of the disease. In practically all instances the persons affected were engaged in a cleaning project involving agitation of long-undisturbed dry dusty materials containing excreta, mostly avian, within restricting enclosures. Fungal isolations from soil samples collected at the point source of the epidemic have been successful in 16 of the 21 outbreaks.

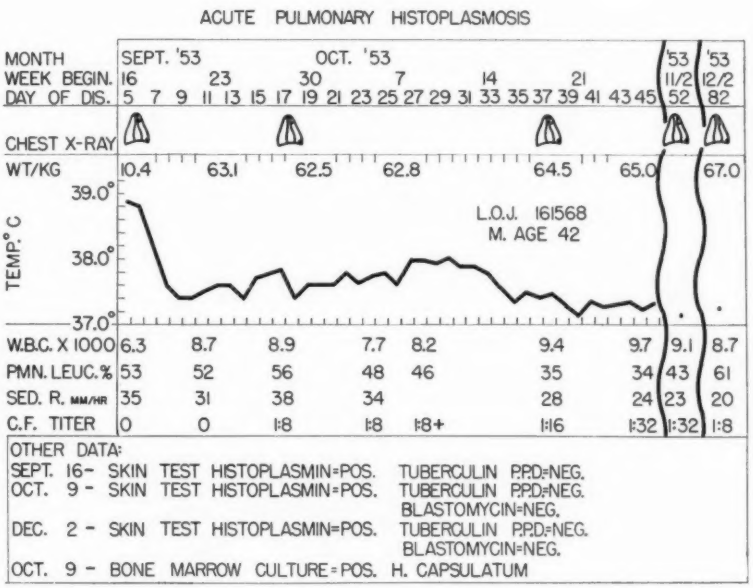


FIGURE 1. Characteristic clinical course and laboratory data of a patient with acute pulmonary histoplasmosis. (Chest roentgenograms of this patient are shown in figure 7.)

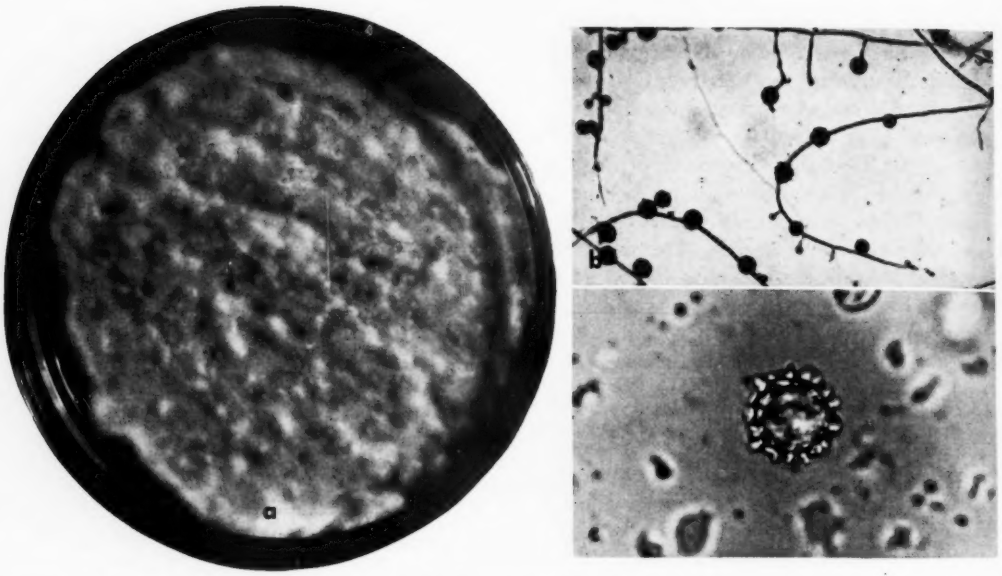


FIGURE 2a. Mycelial growth of *H. capsulatum*. b. Characteristic tuberculated chlamydospores on short stalks attached to branching mycelia. c. Single enlarged chlamydospore with typical tubercles about circumference.

Course of Disease

The symptomatology of histoplasmosis may be insignificant to severe, very occasionally progressing to chronicity or fatal dissemination. It offers us little to distinguish the disease from other febrile illnesses (figure 1). Asymptomatic cases do occur, but usually the symptoms are "flu"-like. The incubation period is probably anywhere from 7 to 21 days dating from the inhalation of the fungal spores. There are fever, chills, headache, backache, malaise, anorexia and usually a cough with or without sputum. Physical examination of the chest is remarkable for the paucity of findings even when there is widespread pulmonary infiltration. With an acute attack, the symptoms usually abate in a few weeks or less. Fatigability may be more lasting. The pulmonary lesions go on to heal, sometimes by resolution over weeks or months or by calcification over many years. Patients whose disease progresses to chronicity with cavitation may continue to have cough productive of sputum, usually positive for the fungal agent. These patients may remain satisfactorily in balance with their disease for many years. Others may progressively go downhill. Acute dissemination of the organism throughout the reticulo-endothelial system inevitably ends in death.

Etiologic Agent

The responsible fungal organism, *H. capsulatum*, has a dual personality, being both saprophytic and parasitic. Saprophytically it grows in nature as a fluffy white mycelium of benign appearance (figure 2a). However, it has never been found to grow obviously in its natural habitat. Only a nutritiously poor laboratory medium such as cornmeal extract agar makes a luxuriant mycelial growth possible. Magnification of such mycelia provides the diagnostic identification of the characteristic tuberculated chlamydospores attached to short stalks of the straightly branching mycelia (figure 2b). The tubercles about the circumference of the mature chlamydospore resemble the petals of a sunflower (figure 2c). By becoming air-borne, such spores may be inhaled by human or animal. Once in the lung, the organism quickly adapts to its new environment by converting to the parasitic yeast form.

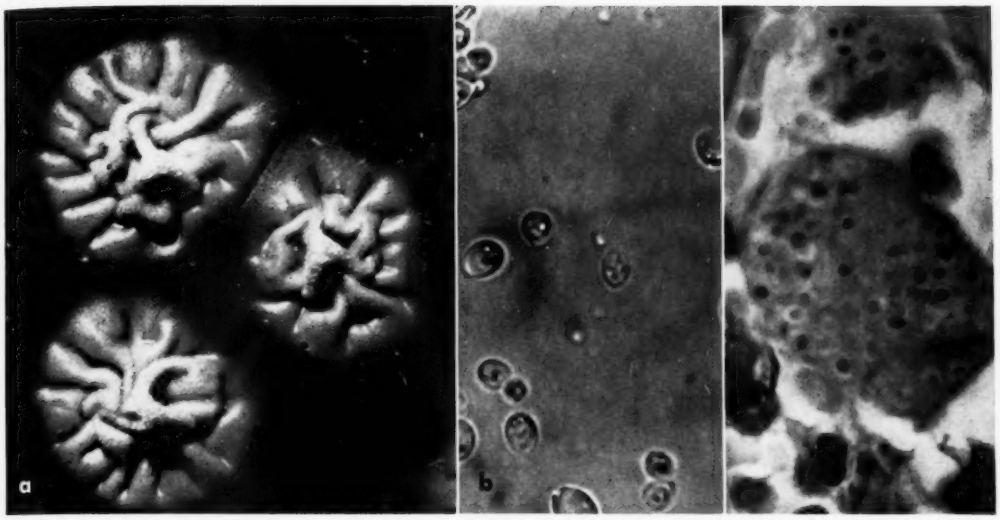


FIGURE 3a. Highly magnified cerebriform colonies of *H. capsulatum* yeast phase. b. Encapsulated individual and budding yeast cells of *H. capsulatum* in saline suspension. c. Several macrophages of the spleen, engorged by encapsulated yeast cells; patient succumbed to generalized histoplasmosis.

This parasitic or pathogenic yeast phase of *H. capsulatum* provides for rapid multiplication. Ingestion of these organisms in turn by the macrophages of the reticulo-endothelial system provides the pathologist with the classic slide showing the intracellular encapsulated organisms literally engorging these cells (figure 3c). A typical culture of the yeast phase on cysteine- and dextrose-enriched blood agar consists of discrete round colonies with furrowed or cerebriform surfaces (figure 3a). Pyramiding at the center, with furrows radiating out from the center, is common. The color of the colony is a lustrous tan with a tendency for surface mycelial growth as aging takes place. A suspension of such a growth in saline reveals microscopically that it consists of millions of individual encapsulated single or budding typical yeast forms—the same forms that engorge the macrophages of the infected individual (figure 3b).

Disease Spectrum—Case Examples

Since the clinical spectrum of histoplasmosis ranges from inapparent infection to a fatally fulminating disease, familiarity with its variable patterns can aid in promoting its consideration as a plausible diagnosis. Both in symptoms and by roentgenogram, histoplasmosis is a mimic of many diseases. The great variation, particularly in the pulmonary lesions of this fungal disease, tends greatly to emphasize the need for careful differential diagnosis. The differentiation of tuberculosis and histoplasmosis presents the greatest challenge. Other fungal infections, lung metastases, neoplasm, lymphoma, sarcoidosis and virus pneumonia are but a few additional differential diagnoses to be entertained. Reports of some typical cases of histoplasmosis to cover this wide spectrum follow.

Asymptomatic primary infection—This is the most benign of the histoplasmosis infections. Usually it would be a chance diagnosis. It simulates mostly asymptomatic tuberculosis infection with development of a primary complex which is detected roentgenographically many years subsequent to the infection. A 17 year old girl who was infected in a small epidemic outbreak[10] of histoplasmosis represents such a case. Though she had no clinical illness, her histoplasmin skin test was positive

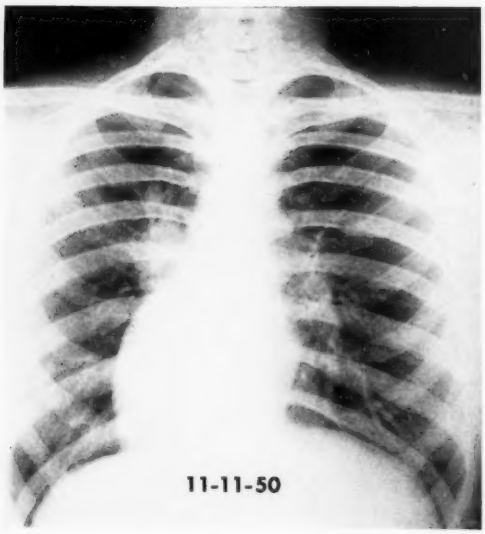


FIGURE 4. Asymptomatic primary infection with *H. capsulatum* resulting in a left hilar infiltrate.

FIGURE 5. Histoplasmoma or coin lesion in left lower lobe, usually asymptomatic. Surgical biopsy confirmed the diagnosis.

and her complement fixation test was 1:20. Presumptively she had histoplasmosis. A definite left hilar infiltrate was present at the time other members of her family were very ill with proved pulmonary histoplasmosis (figure 4). Within six months her roentgenologic findings had cleared. The primary histoplasmosis complex probably develops asymptomatically in just such a way in many persons living in the endemic area.

Asymptomatic histoplasmoma—This lesion, often called a coin lesion, usually is discovered on a routine chest roentgenogram. Such a case concerned a 52 year old woman without symptoms (figure 5). The histoplasmin skin test was positive but the complement fixation test for antibodies to *H. capsulatum* was negative, as is usual with such walled-off lesions. In view of the threat of neoplasm in the older age group, it was decided to remove the lesion surgically. Biopsy demonstrated a nodular, calcium-ringed, caseous-centered granuloma. Staining by the Gridley technic disclosed the ghosts of *Histoplasma* yeast cells crowded within the caseous center of the nodule.

Acute febrile pulmonary histoplasmosis—The next two cases are examples of the acute form of histoplasmosis. The first is a laboratory-incurred infection in a 35 year old physician engaged in research work with the *H. capsulatum* organism.[11] The known exposure, the conversion of the histoplasmin skin test from a negative to a strongly positive reaction early in the febrile illness, together with a rising titer of complement-fixing antibodies to *H. capsulatum*, furnished presumptive diagnostic evidence. A chest roentgenogram revealed a prominent linear density in the right lower lobe which gradually resolved over a seven month period (figure 6a, b). Complement-fixing antibody titers rose acutely during the illness and disappeared with resolution.

Another case of acute pulmonary histoplasmosis in a physician, aged 42, was definitely proved by culturing *H. capsulatum* from the bone marrow. The acute febrile illness was quite brief, but a low grade fever was more persistent (figure 1). Skin testing gave a positive reaction to histoplasmin but a negative reaction to tuberculin. The complement fixa-

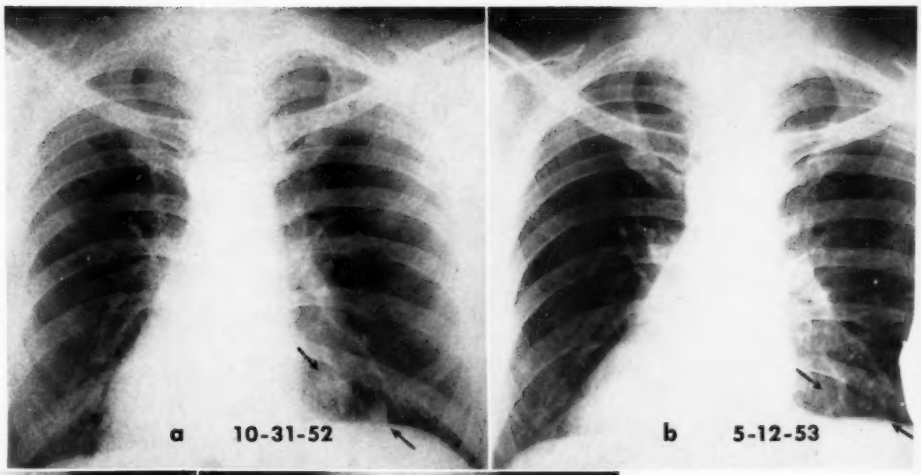


FIGURE 6a. Acute febrile pulmonary histoplasmosis with right lower lobe infiltration. b. Resolution of lesion over period of seven months.

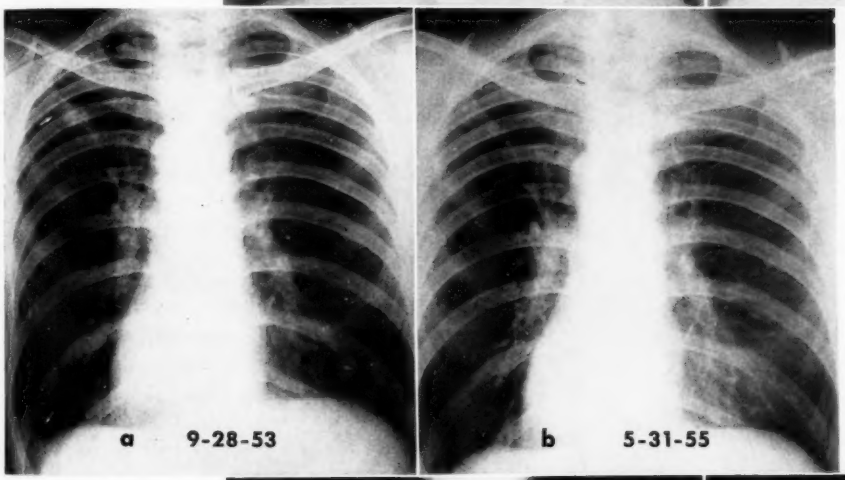


FIGURE 7a. Acute pulmonary histoplasmosis resulting in two well-circumscribed infiltrates in the right lung field. b. Noncalcified residual faint infiltrates remaining 21 months after the acute illness.

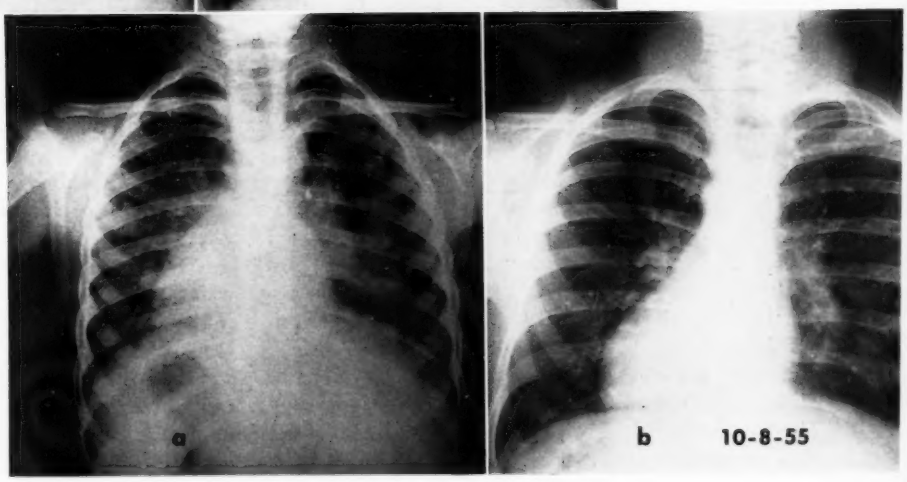
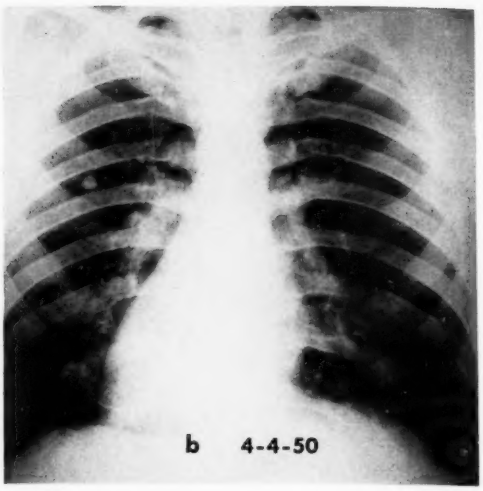


FIGURE 8a. Acute diffuse pulmonary histoplasmosis in a child. b. Healing of the lesions over a five year period resulted in miliary calcification.



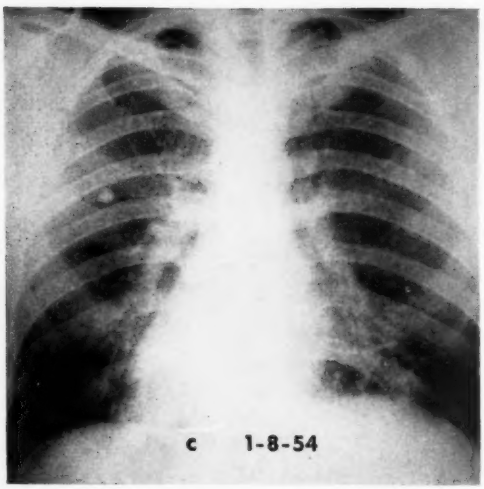


FIGURE 9a. Normal chest. b. Persistent discrete nodule in left lung field with conversion of tuberculin skin test to positive. c. Diffuse pulmonary histoplasmosis superimposed on single discrete tuberculous lesion.

tion titer became positive by the second week of illness, rose steadily to the end of the second month, then fell gradually to the low value of 1:2, which has persisted for two and a half years. His chest roentgenogram demonstrated two discrete circumscribed infiltrates in the right lung field, one in the upper lobe and the other just above the diaphragm (figure 7a, b). After 21 months faint noncalcified infiltrates remained.

Acute diffuse pulmonary histoplasmosis—The more massive form of the disease, which goes on to healing by resolution or calcification, or both, is demonstrated by the case of a five year old boy who was infected in an epidemic outbreak.[10] He had an acute febrile illness resulting in a positive histoplasmin skin test and a positive complement fixation titer of 1:160. A chest roentgenogram during his acute illness revealed very diffuse pulmonary infiltration bilaterally (figure 8a, b). Calcification of these lesions began within six months after the acute illness. With further progressive calcification the lungs have become literally filled with buckshot. This case should call to mind how frequently such roentgenographic findings have been ascribed—mistakenly, of course—to healed miliary tuberculosis.

A similar case of acute diffuse pulmonary histoplasmosis was that of a 35 year old man whose roentgenologic history is most interesting (figure 9a, b, c). In 1941 he had a normal chest roentgenogram. In 1942 a small discrete infiltrate was found in the middle third of the left lung field and a tuberculin skin test became positive. The lesion persisted for more than 10 years. Infection with *H. capsulatum* occurred in late 1953 during a small epidemic resulting from exposure to *Histoplasma*-infected chicken compost mate-

FIGURE 10. Chronic cavitary histoplasmosis, right apex.

rial used as fertilizer.[12] Symptoms were acute with cough, fever, chills and malaise. The histoplasmin skin test and complement fixation test became positive. There resulted a snowstorm of finely stippled, diffuse bilateral pulmonary infiltration roentgenographically. Clearing took place slowly over the next few months. Calcium will probably be laid down slowly, as has been found to take place in older persons. Such a case pointedly demonstrates a solitary tuberculous lesion on which multiple histoplasmosis lesions have been superimposed. The miliary reseeding of tuberculosis could be a tempting diagnosis if the facts of the case were unknown.

Chronic cavitary pulmonary histoplasmosis—In order of progression to the more disabling aspects of this disease, the chronic cavitary lesion follows, complicating the differential diagnosis even more. Such a case is that of a 58 year old man who had been chronically ill for five years.[13] His sputum was persistently positive for *H. capsulatum*, while tubercle bacilli could not be isolated. Tuberculin and histoplasmin skin tests were positive. The complement fixation test was positive at a persistent titer of 1:40. A chest roentgenogram demonstrated cavitating disease in the right apex (figure 10). The diseased upper lobe was excised, and the biopsy specimen showed the cavity wall to be rimmed with numerous macrophages (figure 11a), which were loaded with the encapsulated yeast phase of *H. capsulatum*. A direct culture from the cavity wall produced a pure growth of *H. capsulatum* (figure 11b).

Even more extensive chronic cavitary histoplasmosis is represented by the case of a 49 year old man whose roentgenograms for over three years have continued to show persistent

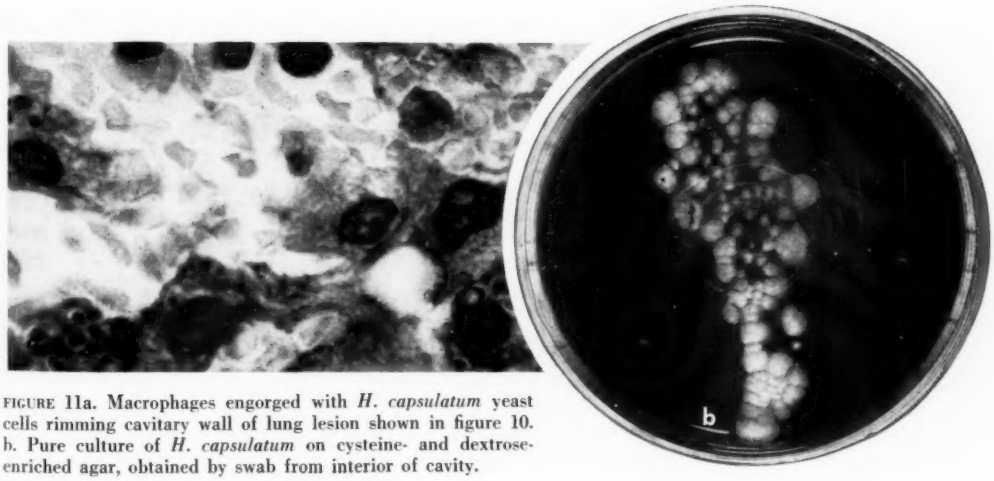


FIGURE 11a. Macrophages engorged with *H. capsulatum* yeast cells rimming cavitary wall of lung lesion shown in figure 10. b. Pure culture of *H. capsulatum* on cysteine- and dextrose-enriched agar, obtained by swab from interior of cavity.

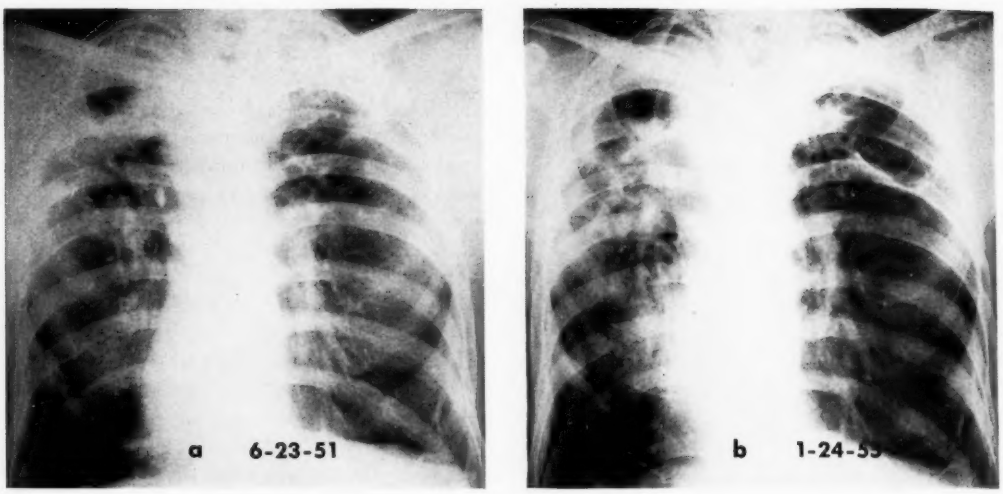


FIGURE 12a. Bilateral apical cavitary histoplasmosis, initial roentgenogram. b. Roentgenogram showing progression of the disease over a span of three and a half years.

bilateral apical disease (figure 12a).[13] The original diagnosis, based solely on roentgenographic findings, was far-advanced active tuberculosis. All cultures for tubercle bacilli were negative, however. Finally, when histoplasmosis was considered as a diagnosis, *H. capsulatum* could be cultured from all sputum specimens (figure 13). Positive complement fixation titers have persisted at 1:64 levels for four years. Through the years, roentgenograms have shown progressive bilateral apical cavitation, even though the patient is able to carry on full-time employment (figure 12b).

Acute histoplasmosis with dissemination—The rare but overwhelming form of the disease in which there is dissemination throughout the reticulo-endothelial system, resulting in death, represents the extreme of the disease spectrum. An example is the case of a 63 year old man whose disease was extremely debilitating, with death occurring in four months. Enlargement of the organs of the reticulo-endothelial system was notable. In such an overwhelming infection, the histoplasmin skin test and complement fixation test often remain negative, as they did in this instance. Thus, some of our diagnostic procedures fail us when greatly needed. The chest roentgenogram was a picture of massive infiltration bilaterally (figure 14). Sputum smears containing macrophages engorged with the yeast were conclusively diagnostic (figure 15a). The autopsy specimen of the lung showed almost complete involvement of the macrophages, the fungal organism predominating (figure 15b).

FIGURE 13. Pure culture of *H. capsulatum* directly from sputum of patient whose chest roentgenograms are shown in figure 12.

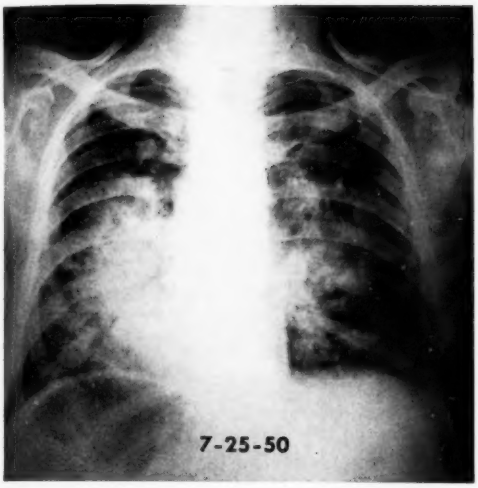


FIGURE 14. Acute disseminated histoplasmosis in an adult, with massive bilateral pulmonary infiltration.

The case of a 10 year old boy demonstrates an even more acute case of fatal disseminated histoplasmosis of only four weeks' duration. Lymphadenopathy with hepatosplenomegaly were prominent. The complement fixation test and histoplasmin skin test were positive in this instance. The bone marrow culture was strongly positive. Again, the lung fields were diffusely infiltrated (figure 16). Microscopic sections of the liver, spleen and adrenals revealed macrophages engorged with the encapsulated yeast of *H. capsulatum*.

Diagnostic Procedures

With due respect to these examples of infection, how could a physician possibly omit histoplasmosis from his differential diagnosis for a pulmonary infiltration occurring in a patient living in the endemic area? As a lung disease it is a great imitator. In addition, histoplasmosis can be only a localized infection, with lesions affecting the skin, mouth, tongue, larynx, eye or joints. Once suspicions are aroused from the history, physical and roentgenographic findings, proof rests in pursuing the following diagnostic procedures:

1. Culture
   a. Direct plating
   b. Mouse passage
2. Serologic tests
   a. Complement fixation
   b. Precipitin
   c. Collodion agglutination

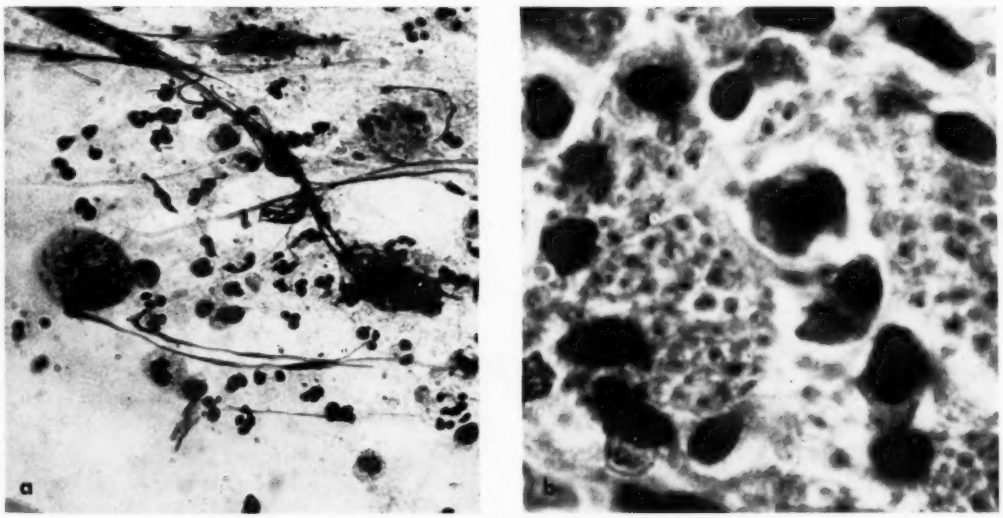


FIGURE 15a. Sputum smear showing free macrophages containing *H. capsulatum;* same patient as in figure 14. b. Pathologic section of consolidated lung of same patient, illustrating the overwhelming involvement of macrophages.

FIGURE 16. Acute disseminated histoplasmosis with diffuse pulmonary involvement in a child.

3. Skin test
4. Examination of tissue
   a. Biopsy
   b. Autopsy

Isolation of *H. capsulatum* by direct culture onto suitable media or by means of mouse passage remains the only definitive proof of the disease. Sputum, gastric washings, bronchial secretions, blood, bone marrow, exudates and biopsy materials could all be subjected to culture.

Many times throughout this presentation, the histoplasmin skin test and the complement fixation test for antibodies to *H. capsulatum* have been cited as diagnostically important. The complement fixation test and its reflection on the disease pattern are noteworthy. An interjection in regard to this test might clarify its usefulness. A killed whole-yeast suspension of *H. capsulatum* organisms is used in a standard complement fixation titration to determine the titer of antibodies in the patient's serum to this antigen. In our experience, positive titers mean some activity of the disease and can reflect the disease pattern.

In general the more acutely ill patients have higher titers that slowly fall to negative with resolution and healing. In milder cases there are lesser rises in titer. The highest antibody titers are usually reached in a few weeks after the onset of the illness but fall slowly to negative over a period of months or years with healing. In chronic cases the titer is persistent, though debilitation may not allow a titratable antibody response. Overwhelming acute histoplasmosis also may not elicit an antibody titer. The greatest value of any serologic test results from serial serum titrations in an attempt to demonstrate the initiating or rising or persisting or falling of an antibody titer. Prognostic information is also thus obtained.

The precipitin and collodion agglutination tests as serologic procedures are used less often by diagnostic laboratories than is the complement fixation test, but they provide similar information.

Brief mention must be made of the existence of cross reactions in the serologic diagnosis of histoplasmosis, coccidioidomycosis and blastomycosis. However, further discussion will

not be presented on this interesting facet of the relationship of these fungi in their antigenic properties.

The histoplasmin skin test has the same significance as the tuberculin skin test. It implies either an old exposure or active disease but will not distinguish between the two possibilities. A conversion from a negative to a positive reaction during an acute febrile illness has great diagnostic importance. If the skin test remains negative, the diagnosis is quite untenable except in debilitating disease. Explicitly it can be said that cross reactivity never exists between tuberculin and histoplasmin as skin-test antigens.

Microscopic examination of tissues as a diagnostic procedure deserves no particular comment.

Conclusion

As physicians, one of our duties includes the greater and more accurate recognition of the fungal disease histoplasmosis. Awareness of its existence and its common occurrence in the Midwest States would aid us in this recognition. Proof will be lacking unless proper diagnostic evaluation is undertaken.

I am indebted to my associates, Dr. Clayton G. Loosli and Dr. D. F. Loewen, for permission to publish the chest roentgenograms of a number of cases which are part of a cooperative long-term study of this disease.

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MEETINGS *and Postgraduate Courses*

American College of Chest Physicians: The Council on Postgraduate Medical Education will sponsor the following postgraduate courses on diseases of the chest:

Eleventh annual postgraduate course, Hotel Knickerbocker, Chicago, October 15-19

Ninth annual postgraduate course, Park-Sheraton Hotel, New York, November 12-16

Further information may be obtained by writing: Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Harveian Society of London Tercentenary Commemoration: Review of present knowledge of the circulation, June 3-8, 1957, at the Royal College of Surgeons, London, England. Proposed subjects include the circulation from the seventeenth to twentieth centuries, regulation of the circulation, results of cardiac surgery, and coronary, pulmonary, cerebral, splanchnic and peripheral circulation.

University of Minnesota, Minneapolis: Courses to be presented at the Center for Continuation Study, Fall 1956:

Pediatrics for pediatricians, September 25-27
Technics in general practice, October 18-20
Gynecology for general physicians, October 22-24
Radiation therapy for radiologists, November 5-9
Fractures for general physicians, November 19-21

University of Texas Postgraduate School of Medicine: Postgraduate medical cruise to the Caribbean, February 8-22, 1957. The Antilles of the French Line will leave from Galveston. Ports of call include Port-au-Prince, Kingston, Curaçao, La Guaira, Cristobal and Havana. One professor each in surgery, internal medicine, pediatrics, cardiology and obstetrics and gynecology will accompany the group. Additional information may be obtained by writing Mr. D. Stuart Godwin, Jr., Harvey Travel Bureau, 2005 West Gray, Houston.

Helping the Physically Handicapped Child to Face the World

RUTH MORRIS BAKWIN*

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A HANDICAPPED child has been defined as "any child who has a physical or mental defect which prevents him from taking part freely in the activities so important to all children." Not included are children who have found a way of living comfortably with minor peculiarities.

RUTH MORRIS BAKWIN

There are no good statistics on the number of handicapped children but recently, since parent groups have been formed, the number of cases reported has greatly increased. Probably about 5 per cent of all children are handicapped physically and over 1 per cent have mental limitations which call for special schooling. Of about 53 million children in the United States, at present, there are more than three million physically or mentally crippled.

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The Parents' Reaction

The presence of a handicapped child in a family is always a shock and cause of grief and anxiety. Families secure in their relationships with one another can cope with the situation with greater success. The child's behavior difficulties have been found to be more often a response to parental attitudes than a reaction to the physical disability as such. The most desirable parental behavior has been defined as "objective"—that is, the realistic acceptance of the child's behavior limitations, with sufficient care and affection to provide security for the child but not so much as to give rise to emotional dependency.

The parents of a child with a crippling disease or incapacitating handicap at first experience a period of grief mixed with shame, guilt, rebellion and despair. The question, "Why did this happen to us?" recurs repeatedly. To have produced a child with a deformity is frequently taken by the parents as evidence of their personal inadequacy; in some way they feel responsible and to blame. Occasionally, as in cousin marriages or when a parent

has a hereditary condition such as deafness, there may be some parental responsibility, but the great majority of cases of congenital disability or crippling are not in any way the fault of the parents or ancestors. Nevertheless, guilt and shame are prominent parental attitudes. At times the blame is projected onto others—the obstetrician or some member of the family who is not perfect. Occasionally it is projected onto society in general.

Many parents feel resentment at their child's misfortune and are unable to adjust to his presence. Parents accept more readily the disabling of a child already known and loved than when this occurs in a newborn or young infant.

Concern over neighbors' opinions of their child or of themselves, with fear of ridicule or pity, is another common attitude which may cause the parents to withdraw from society or to attempt to hide the fact that their child is crippled.

These attitudes manifest themselves in different intensities and in various ways depending on the type of handicap, its severity, the personality of the parents and the age of the child when crippled. The child, too, takes an active part in the parent-child relationship.

The parent builds up defense mechanisms as technics to cope with the handicapped child. (1) Most common among these is overprotection of the child and prolongation of his infantile dependency. The handicapped child's helplessness becomes more plausible when the parent can continue to regard him as a baby. (2) There may be overemphasis and exaggeration of the child's intellectual capacities. If the child is mentally normal or superior, his physical inferiority can be more easily accepted. (3) Preoccupation with and overdependence on rehabilitation are ways by which the parents convince themselves and others that everything possible is being done for the child. (4) The parents justify prolonged hospitalization by saying that the child is too large to handle properly at home, or that he is happier with the group, or that the mother is not, at the moment, well enough to take him home. (5) Sublimation is sometimes accomplished by exaggerated activities with the group, such as raising money for the hospital, or trying to change legislation regarding the education of crippled children, or working for the Cerebral Palsy Association or the Heart Fund.

In some instances there is distaste for the crippled child's appearance and rejection by the parents on this basis. Or the expense and need for long-time treatment may appear so impossible to meet that the parents wish they had no child. Hope for the future disappears in despair at the child's slow progress, and the parents may dislike the child for upsetting their lives and the lives of the entire family.

As with healthy children, parental rejection may be conscious and overt, as when they criticize the child's behavior and he becomes antagonistic, but more often the rejection is unconscious. The parent feels unable to give love and affection but is willing to spend time and money on rehabilitation, nursing care and hospitalization, sometimes in exaggerated amounts. This, of course, does not mean as much to the child as being accepted and wanted.

Helping the Parents

The parents may be helped in many ways. They should be reassured that the child's disability is not their fault. This may have to be reiterated frequently before it is accepted. In some instances it is possible to explain how the condition occurred and what it really is. Thus the parent need blame neither himself nor others. Realistic understanding by each parent of his child's present status in relation to his handicap, as well as some idea of future expectations, will help to relieve anxiety and allow the child to develop to his optimum level.

Group discussion is of value in minimizing the parents' feeling of isolation and difference and also in demonstrating that their attitude toward the child in no way differs from that of other parents toward their handicapped children. This brings reassurance and relief of guilt. Group activities will help to channel parental feelings and attitudes constructively. An analysis can be made of the child's emotional, social and educational needs and suggestions made as to how they may best be met.

The crippled child's role in the family can be discussed and technics planned for neighborhood participation.

The Child's Reaction

Parental attitudes are apt to be extreme. Their feelings are usually a confused mixture of protection, tenderness, hostility, rejection and pity. Children differ in their innate capacity to react with anger, aggressiveness, self-dependence and courage.

The presence of a physical handicap frequently leads to feelings of inferiority and of insecurity in the child. It threatens personality development by interfering with his normal activity and by isolating him from other children. It fosters parental overprotection and oversolicitude which keep the child immature. The handicapped child feels different from other children. The desire to conform usually appears at school age, but when a physical defect is present it may manifest itself earlier. There are two personalities in the disabled person, fighting with each other—the one he was basically, with all the potentialities and desires of the healthy individual, and the one resulting from damages due to his handicap. These two must be integrated before he can become emotionally adjusted. This is accomplished when the individual accepts his handicap and evaluates his potentialities.

Some children accept the anxious, overprotecting attitude of the parents, becoming submissive, dependent and perhaps apprehensive. They wish to be helped and catered to and remain infantile and immature. Temper tantrums are frequent when parental response is not prompt enough.

Other children more often react with anxiety. This may be expressed by night terrors, fear of being alone and the need to have the mother constantly at hand.

Still other children rebel, denying illness by exaggeration of activity and refusing to follow directions or carry out treatment. Or rebellion may be manifested by repeated attempts at self-dependence. When the child is unable to succeed in what he tries, he becomes frustrated and disturbed.

Illness and disabilities are sometimes accepted by the child as gratifying experiences because of the attention and care bestowed on him. It is difficult to get these children to make any effort on their own behalf. They appear apathetic and disinterested, except when demanding.

The casual attitude of some parents toward their child's disability may be bewildering to him, who, not appreciating the severity of his handicap, may hold false hopes for full recovery. This attitude prevents the child from facing his special situation realistically.

False sympathy and pity may cover hostility of which the parent is unaware or ashamed, or may be shown by friends and neighbors who unconsciously reject the child. The attitude of the neighbors follows largely on the example of the parents. Harmful misconceptions still persist concerning various disabilities, especially epilepsy.

Treatment Away From Home

In hospital or residential school the child may be deprived for a long time of some of the basic needs of childhood, particularly his home life and family relationships. As much as possible, the parents should keep contact with the child through visits, letters, gifts and telephone conversations. These mean much to the child as indication that he is not forgotten and that his place is being kept for him at home.

Some handicapped children must remain away from home for long periods. Children with orthopedically crippling diseases who need rehabilitation sometimes are in hospitals and rehabilitation centers for months or years. Children with heart disease or tuberculosis often are sent to homes for convalescents for many months following their acute episodes. In many localities there is no adequate schooling for the blind or deaf, except in boarding schools away from home. This experience itself makes the child different from the nonhandicapped child who remains in his home. Adjustment to life with strangers is hard for most children, and may be exceptionally hard if the nurses and teachers are not acquainted with their emotional needs. The person en-

trusted with the responsibility of child care in a residential center should be an affectionate, warm, accepting, helpful, parentlike person. Treatment should be directed toward improving the child's capacity for living in his own home, in his community, and in the world at large.

Home Care

The crippled child cannot go out and take his place among normal children. His activities and self-dependence are limited, so his parents must find ways to compensate. This requires much time and thought. If the crippling is such that it will prevent normal activity throughout life, the problem is to fit the patient to live within a narrower range than the normal child.

The parent is faced with many problems. His lot is made easier by an early diagnosis and explanation as to what the disability means. He needs the facts and an understanding of them. He should be helped to accept the diagnosis and plan of treatment. There is a continuing need for interpretation and evaluation of the child's needs at different stages. An entire reorganization of the household may be necessary. Help from relatives, neighbors or organizations may be desirable so that the mother will not become too fatigued or other members of the family be neglected. A regular routine is valuable to both the family and the child.

Education

It is as important to train the child intellectually as it is to treat him physically. When possible, medical treatment and education should be co-ordinated. He should be taught at the level at which he is capable of learning. Some handicaps stem from conditions which also cause decreased mental functioning. This is so in some cases of meningitis which result in deafness and also in brain damage, and in some cases of cerebral palsy where the brain does not function properly intellectually or for motor control.

In other instances the disability may handicap the child so that learning is difficult. Blind children must overcome great obstacles before they catch up in ability with seeing children. Children with unco-ordinated tongue movements have enough difficulty with speech to delay their intellectual achievement. There are more mentally retarded and defective children among the physically handicapped than among nonhandicapped children.

Special schools or private tutors may be advisable, but as soon as possible the child should be placed in regular classes with nonhandicapped children. It may be necessary to see that he has special devices to help him, such as hearing aids, typewriters, readers, etc. Or he may have to sit in the front of the classroom if he is hard of hearing, or on one side if he has poor vision in one eye, or he may have to write his lessons if his speech is unintelligible. In spite of these privileges, the sooner he can join the class with normal children the better his chance for character development.

Helping the Child

The behavior of the child, and his personality, although dependent primarily on his innate personality and on parent-child attitudes, are influenced also by the type of handicap and the need for any special training and education.

Adequate treatment to reduce the disability as much as possible is an important consideration. Then the child should be taught to make good use of his limited ability. The child must not be satisfied with having, instead of doing.

He needs experience and adventure, freedom to move about, to manipulate objects, to learn what goes on in the world, to ride in busses, visit the zoo, see tall buildings, attend concerts and movies, to have all the new experiences compatible with his disability, for in this way he grows and increases his powers.

He should be given as nearly as possible the independence of a normal child, and be permitted to do for himself and for others as much as he can do. The aim should be to make him a working member of society when he reaches adulthood.

Social contacts are important for the handicapped child. Friendships with other crippled children should be encouraged, as in com-

petition with them he has a chance for real (not relative) success. But he needs nonhandicapped friends as well, for he must live in a world of normal people. It is well to learn early to adjust to them. Meeting new people is an adventure and as such is valuable for the child. The help of brothers and sisters should be enlisted. They are most often realistic about the handicap, and their attitude inspires trust and love in the crippled child. They can play with and teach him, give him affection, consideration and understanding.

Parental affection, rightly expressed, provides the child with a solid basis for a healthy emotional life. When the child knows he is wanted and needed, when he can trust his parents and turn to them for help at all times, he will feel confident and secure.

The handicapped child needs a special form of courage and cheerfulness, and to develop this he needs deep understanding and love from those about him. He can be made to feel that he is a respected member of society.

A happy blend of security and adventure will promote emotional stability and growing independence. Sometimes a child can help his parents, if he meets his problem with courage and realistic understanding.

Most parents feel discouragement and despair as they look ahead to the adult life of the severely handicapped child; fortunately the young child lives from day to day and usually not until adolescence is he concerned.

There is much the handicapped child cannot do. If he is blind, he may always need help to get about; if he has cerebral palsy, certain movements may always be an effort and he may be continually conscious of his body. But he should be taught to get the maximum use of whatever he has left. As he grows older, his interests may extend from self-concern to concern for other members of his group, and from there to interest in all people. He thus becomes a giving and contributing individual, with wider human sympathy and a more mature approach to life.

The Adolescent

The adolescent, more than the child, suffers discouragement and frustration. He worries about the future, about friendships with the other sex, his ability to work, marriage, children.

At this age, he can be greatly helped by encouraging him in growing up. He should be urged to become as self-dependent and responsible as possible. He can be given more mature books to read, can become an active participant in discussions of his illness, can take responsibility for his own treatment. Friendships with boys and girls his own age should be encouraged.

Adolescents are idealistic; they are interested in the large issues of mankind. These interests can be utilized for useful work. There are many problems to be solved which can be done in a limited environment, and much research which does not need ambulation or even speech.

Not all handicapped people should marry, but some statistics on the subject are interesting. A survey of over 1800 handicapped and 500 nondisabled workers employed at an aircraft corporation was made in 1946. Some of the workers were severely handicapped, others less so. The mean age was 37 years. The percentage married were:

Handicap	*Men*	*Women*
Auditory	69.0	50.8
Visual	64.0	53.8
Cardiac	61.5	59.4
Orthopedic	51.5	52.0
Average of handicapped	61.0	54.0
Physically normal	71.0	49.0

If the marriage is based on genuine affection and not on expediency or pity, there is a basis for success. After marriage, the decision as to whether or not to have children is a perplexing one. If the handicapped person is capable of being a good parent, with time and desire to help his child, a family may be contemplated. But if his personality is so distorted by his condition that it is unlikely that he will be able to give his child affectionate understanding, it might be unwise.

The disabled person should contribute his share in the world, no matter how small. Tests of aptitude may be of value for proper placement. There are many positions open to him.

Among them, occupation with a craft such as silversmithing, painting or music is one of the most satisfactory, because it assures more independence and less pressure.

Individuals with all types of handicaps have risen above them and not only have lived happy, useful lives but many have been outstanding in their contributions to every field of work. Mention need be made only of Beethoven, Edison and Helen Keller.

Many of the problems occurring in association with the handicapped child, due to mismanagement, could be avoided. For optimal emotional growth and development the handicapped child, like any other child, must be helped to grow according to his own individual plan and must feel that he is needed and wanted in his home, that he is a part of his group in play, in school, or in the hospital—that is, he must feel he belongs. Then he will become self-reliant and develop confidence to face his problems as they arise.

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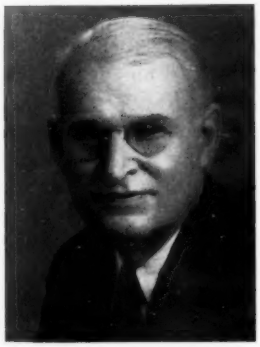

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A Survey of Estrogens

EDWARD B. CANTOR

Sherman Oaks, California

THE purpose of this article is to review the physiology and clinical applications of estrogens, for the benefit of practicing physicians who may be perplexed by the sundry new products constantly being introduced by the manufacturers of hormones.

EDWARD B. CANTOR

The primary estrogens are produced by the ovarian follicles in the form of α-estradiol, which is excreted in the urine of pregnant and nonpregnant women as estrone and estriol (commercially, THEELIN® and THEELOL®).[1] Estrogen is also found in the corpus luteum, interstitial cells of the ovary, syncytial cells of the chorionic villi of the placenta, and adrenal glands.

The commonly accepted biologic unit of estrogens is the rat unit of Allen and Doisy. Four mouse units or 10 I.U. (International units) is equivalent to 1 R.U. Because of the wide variance in potency, one should not compute dosage of natural or synthetic estrogens on the basis of weight. For instance, estradiol benzoate has a potency of 60,000 I.U. per milligram when given intramuscularly, whereas estrone (Theelin) has a potency of 10,000 I.U. per milligram when given intramuscularly.

How do estrogens affect the various parts of the human body? An estrogen may be defined as any substance that will bring about an increase in vascularity and growth of the vulva, vagina, uterus and fallopian tubes and is also capable of stimulating manifestation of secondary sex characters in the female.

The reddening and swelling which follow the administration of estrogen to children with gonococcal vaginitis illustrate the effect of the hormone on the vulva. Its effect on the vagina consists of thickening of the squamous epithelium, increase in the glycogen-containing epithelial cells, reduction of the pH of the vaginal secretions, and cornification and desquamation of the superficial cells. The cytoplasm of the desquamated cells becomes free of granules, and the nuclei are either small, fragmented or absent.

Adequate doses of estrogens produce growth and increased vascularity of the human uterus. Consequently, marked improvement follows their use in some cases of uterine atrophy. Occasionally, an atrophic endometrium may be

TABLE 1

EFFECT OF ESTROGENS ON FEMALE ORGANS

Vulva	Increase in vascularity
Vagina	Increase in vascularity, thickening of squamous epithelium
Uterus	Increase in vascularity and growth; can convert atrophic endometrium to hyperplastic one
Fallopian tubes	Increase in vascularity, growth and peristalsis
Urinary bladder	Increase in vascularity and growth of vesical sphincters
Anterior lobe of hypophysis	Small doses may stimulate pituitary gonadotropic hormones; large doses suppress pituitary activity
Ovary	No important direct effect; may cause secondary regressive changes in structure and function due to suppression of pituitary gonadotropic hormones

converted into one that undergoes monthly cyclic changes.

Prolonged use of excessive amounts of estrogen suppresses ovulation and menstruation by inhibiting the anterior lobe of the hypophysis, since the pituitary gland normally controls ovarian rhythm. Withdrawal bleeding takes place from the estrogen-primed endometrium when estrogens are discontinued. The menses that follow assume a normal character. In the early preovulatory stage, a dose of 0.25 mg. diethylstilbestrol daily for 10 days may delay ovulation and the menstrual flow up to nine days, but in the postovulatory period large doses will not delay menses if given only for a few days.

The fallopian tubes of castrated animals respond to administration of estrogens with enormous growth and vascularity associated with increased peristalsis. Geist and co-workers[2] succeeded in producing peristalsis in previously quiescent fallopian tubes of women in the postmenopausal age group by giving them large doses of this hormone.

The urinary bladder sphincter is related to the vaginal musculature both anatomically and embryologically. Thus, senile atrophy of vaginal muscles incident to estrogen deprivation probably is reflected in the atony of the vesical sphincters of postclimacteric women, which occasionally results in incontinence without apparent cause. By giving large doses of estrogen, Salmon and associates[3] obtained relief of incontinence, dysuria and frequency of urination in a number of these cases.

Estrogens may suppress the anterior lobe of the hypophysis or increase its activity, depending on the dosage and duration of their use. Small doses given over a prolonged period may increase pituitary activity, whereas large doses over a long period inhibit the gonad-stimulating function of the gland. The lack of estrogen inhibition of the anterior hypophysial lobe, as seen in women past the menopause, results in increased output of F.S.H. Thus, during the menopause, the F.S.H. may be increased to such an extent due to primary ovarian failure and consequent reduction of estrogen that a pregnancy test may give a false positive result.

Except for the role they may play in the initial growth of the preantral follicle, estrogens do not influence the ovary directly, regardless of the dose and length of administration. Because of pituitary inhibition, however, prolonged estrogen therapy in large doses does cause secondary regressive changes in ovarian structure and function. Such changes are temporary and do not jeopardize future fertility.

Whether or not estrogens have a carcinogenic effect in persons who have a tendency toward malignancy is still a debatable question. Hertig reported on a series of patients with uterine hyperplasia in whom endometrial carcinoma developed subsequently. Emge and I reviewed 343 cases of carcinoma of the fundus at Stanford University Hospital and found only 11 cases of concomitant carcinoma and endometrial hyperplasia. Zondek reported in 1947 that he had not observed a single case of malignancy attributable to estrogen therapy in 20 years of experience with the hormone. Novak, however, reported a case in which hysterectomy revealed histologic transitional stages between benign hyperplasia and adenocarcinoma; the patient was a 62 year old woman who had taken 1 mg. of stilbestrol every night for 14 years.

I do not prescribe estrogens for women who

TABLE 2

POTENCY OF COMMONLY USED ESTROGENS

	INTRAMUSCULARLY *(I.U. per milligram)*	ORALLY *(I.U. per milligram)*	CLINICAL EFFICACY
Natural estrogens			
Estradiol	120,000	8000	Too rapidly inactivated
Estradiol benzoate	60,000	Not available	Good; more slowly absorbed than estradiol
Estradiol dipropionate	30,000	Not available	Very good; slow absorption rate
Estrone	10,000	2000	Low potency
Estriol	Not available	3500	Low potency
Premarin	Not available (available for intravenous use)	3500 (Mazer) 8000 (Hamblen)	Good; likely to produce uterine bleeding
17-Ethinyl estradiol	Not available	100,000	Most potent of all estrogens
Synthetic estrogens			
Diethylstilbestrol	50,000	10,000	Good; toxic in large doses in nonpregnant women
Dienestrol	50,000	10,000	Good; economical, relatively nontoxic
Vallestril	Not available	20,000 (?)	Low toxicity; absence of withdrawal bleeding

have had surgery because of carcinoma of the genitalia or breasts, or who have had fibromyomas over 6 cm. in diameter, fibroadenoma of the breast, or surgery for endometriosis. I refrain from employing this hormone in patients of the menopausal or postmenopausal age group who have endometrial hyperplasia, but I do prescribe estrogens for endometrial hyperplasia in women of childbearing age.

For all practical purposes, there are two types of estrogens available commercially, the natural and the synthetic. To ascertain which drug one should use for a particular clinical condition, it is necessary to understand and evaluate certain basic essentials concerning the various products.

Natural Estrogens

Estradiol or dihydrotheelin in its oily preparation is inactivated too rapidly to be useful clinically. It has a potency of 120,000 I.U. per milligram intramuscularly and 8000 I.U. per milligram by mouth. Estradiol benzoate (PROGYNON-B®, OVOCYLIN® benzoate or DIMENFORMON® benzoate) has a strength of 60,000 I.U. per milligram when given intramuscularly and is absorbed more slowly than estradiol. Estradiol dipropionate (Ovocylin dipropionate, Dimenformon dipropionate) has half the potency of estradiol benzoate but is more slowly absorbed. Estrone (Theelin, MENFORMON®) has a potency of 10,000 I.U. per milligram intramuscularly and 2000 I.U. per milligram orally.

Estriol, commercially known as Theelol, is the weakest of all natural estrogenic substances, having a potency of only 3500 I.U. per milligram when given orally. It is not available for hypodermic injection.

PREMARIN®, a conjugated natural estrogenic substance which is widely used, is quite efficacious in controlling hot flashes, sweating and chills of the menopause. It rarely produces toxic symptoms, but withdrawal bleeding is common following its use. Mazer reported the strength of Premarin as 3500 I.U. per milligram when given orally. Hamblen found that 1.25 mg. of Premarin is equivalent to 1 mg. of diethylstilbestrol, a potency of 10,000 I.U. Premarin is not administered in-

tramuscularly, although Greenblatt has given it intravenously in doses of 20 mg. every 6 to 12 hours for two to four doses to treat dysfunctional uterine bleeding.

The most potent of all natural estrogenic substances is 17-ethinyl estradiol (ESTINYL®, LYNORAL® or ETICYLOL®), which is not available for hypodermic use but in its oral form is 10 times more potent than stilbestrol, yielding 100,000 I.U. per milligram. Mazer has reported that 10 per cent of white patients receiving Estinyl experienced nausea and vomiting.

Synthetic Estrogens

The most widely publicized synthetic estrogen at present is diethylstilbestrol. Given intramuscularly, it has a potency of 50,000 I.U. per milligram; orally, it yields 10,000 I.U. per milligram. Compared with the natural estrogens, it is highly toxic. With a dose of 2 mg. or more, the incidence of nausea, vomiting, epigastric pain, headache, diarrhea, dermatoses and malaise has been reported to be as high as 21 per cent. Doses not over 0.5 mg. by mouth daily, or intramuscularly every fourth day, will cause nausea and vomiting in 3 per cent. It is best to start a patient with a dosage of 0.1 or 0.2 mg. of diethylstilbestrol.

Diethylstilbestrol evokes uterine bleeding with lower dosage levels than do the natural estrogens, and this may be a distinct disadvantage when it is administered to women of menopausal age. For women who can tolerate it, diethylstilbestrol controls the sweats, flushes and chills of the menopause effectively, but it does not control headache, dizziness, depression or insomnia. Most pregnant women tolerate huge doses without vomiting or toxic effect.

Dienestrol, a very potent oral synthetic estrogen, has an advantage over products such as diethylstilbestrol in that it rarely produces nausea or withdrawal bleeding. Its potency is believed to be about the same as that of stilbestrol. In my opinion it is a very good source of estrogens, and I have used it for a variety of clinical conditions. In cases of amenorrhea, however, it is not as efficacious as other types of estrogens because it rarely produces withdrawal bleeding.

VALLESTRIL®, one of the more recently introduced synthetic oral estrogens, is relatively nontoxic and does not cause withdrawal bleeding from the uterus. It has been computed to be from 10 to 100 per cent more potent than estrone.

TABLE 3

SPECIFIC INDICATIONS FOR USE OF ESTROGENS AND THE PRODUCTS ADVOCATED

INDICATIONS	PRODUCTS
1. Gonococcal vaginitis	Dienestrol
2. Amenorrhea (atrophic endometrium)	Estradiol benzoate-Estinyl
3. Deficient cervical mucus	Diethylstilbestrol
4. Dysmenorrhea	Estinyl
5. Endometriosis	Diethylstilbestrol-dienestrol-Estinyl
6. Dysfunctional bleeding	Premarin
7. Anovular menstruation	Estinyl may aid a small number of cases (Brown and Bradbury)
8. Threatened abortion	Progynon-B-diethylstilbestrol
9. Suppression of lactation	Stilbestrol
10. Missed abortion	Dienestrol
11. Surgical menopause	Estinyl-dienestrol-Menformon-estradiol pellets
12. Migraine due to F.S.H. hyperactivity	Dienestrol-stilbestrol
13. Senile vaginitis	Diethylstilbestrol vaginal suppositories-Premarin cream
14. Menopause	Dienestrol-Estinyl-Menformon
15. Menopausal osteoporosis	Dienestrol-estradiol benzoate
16. Senility	Estradiol benzoate-dienestrol

Clinical Applications

In cases of resistant or stubborn gonococcal vaginitis not responding to penicillin alone, 0.1 mg. of dienestrol every day for four to six weeks combined with three daily injections or 400,000 units of penicillin is quite effective. However, one should allow five weeks to elapse after cessation of therapy before pronouncing a case cured. A small percentage of girls will have withdrawal bleeding, but this is only temporary. I have not found it necessary to use estrogen suppositories in these cases.

Numerous methods of administering estrogens and progesterone have been employed to induce cyclic bleeding in cases of amenorrhea. Kaufman has used 100,000 I.U. of estrone (1.66 mg. estradiol benzoate) every third day for five consecutive doses. The day after the fifth dose, the patient receives the first of five daily injections of 10 mg. of progesterone. Kaufman repeats the treatment for three consecutive months, beginning each course on the same date, whether there is a response or not.

To avoid injecting estrogen hypodermically, I prescribe 0.5 mg. of Estinyl every day for 10 to 12 days, followed by 25 mg. progesterone every other day for three doses, repeating this therapy for three consecutive months, beginning each course on the same date. I prefer to administer progesterone parenterally because of the great variability of available oral forms of the product.

The good results of the cyclic form of therapy for some cases of amenorrhea are explained on the assumption that the associated uterine hypoplasia is the sole cause of the condition. Thus the combined steroid therapy stimulates the hypoplastic, atrophic endometrium to activity.

A dose of 0.1 mg. of diethylstilbestrol given daily during the first half of the menstrual cycle has proved effective in treating deficiency of the cervical mucus in sterile women. This treatment will not delay ovulation, but probably will produce a cervical secretion that is more receptive to sperm.

Schuck[4] recently reported a series of 300 patients with severe dysmenorrhea, 60 per cent of whom obtained excellent results with 0.5 mg. of Estinyl daily. The therapy schedule called for starting Estinyl the first day after the end of the menstrual cycle and continuing it daily for 10 to 12 days. He noted that patients who did not obtain relief after the first course of treatment were not improved if subsequent courses were given. If a patient obtained some relief after the first month, Schuck continued treatment for three to five cycles. Such treatment over a period of time resulted in delayed and painless menstruation from an estrogen-primed endometrium. Large doses of estrogen given during preovulatory and postovulatory phases of the menstrual cycle suppress pituitary ovarian function and the natural activity of the myometrium. The delayed uterine bleeding from an estrogen-primed endometrium is not menstrual flow in the physiologic sense of the word, but actually is an estrogen-withdrawal bleeding.

Karnaky and Bickers have been the chief advocates of the use of estrogen in the medical management of endometriosis. This form of therapy suppresses ovulation and menstruation. Mazer cited the case of a patient who became pregnant after a year of amenorrhea caused by continuous stilbestrol therapy. In view of the extreme nausea experienced by so many patients who receive large doses of stilbestrol, perhaps it is best to substitute dienestrol or Estinyl in the medical management of endometriosis. Despite the enthusiasm of Karnaky and Bickers for medical management, I believe that most gynecologists agree with Meigs[5] that conservative surgical treatment is more satisfactory for endometriosis in women of childbearing age. However, both hormonal therapy and surgical treatment have a place in therapy of endometriosis.

In treating dysfunctional bleeding associated with anovulatory menstruation, Greenblatt[6] employed 5 cc. of an intravenous aqueous solution containing 20 mg. of Premarin (sodium estrone sulfate). His series of 56 patients ranged from 15 to 56 years of age. Therapy was repeated every 6 to 12 hours for two to four doses or until bleeding ceased. After the initial control of menorrhagia, 1.25 mg. of

Premarin was given orally four times daily for five days, three times daily for five days, then twice daily for five days, and finally once a day for five days. Bleeding seldom recurred with this diminishing-dosage schedule; when it did recur, the dosage was increased to its former high level, with a satisfactory arrest of bleeding. Following this course of therapy, either 10 mg. of PRANONE® or 10 mg. of LUTOCYLOL® was given three times a day for five days. Then, cyclic oral estrogen-progesterone therapy was instituted for the next four months. None of the patients required more than four injections of 20 mg. of Premarin, and the only untoward effect was occasional nausea which always disappeared after a few days of continuous therapy. The schedule of cyclic therapy employed by Greenblatt consisted of 1.25 mg. of Premarin orally four times a day for 20 days, followed by 10 mg. of Pranone three times a day for five days. Bleeding usually occurred two days after therapy was discontinued. Of a total of 57 courses of therapy given for acute menorrhagia associated with hormonal imbalance, 48 resulted in cessation or lessening of bleeding in 3 to 12 hours after intravenous injection of Premarin. Greenblatt reported a number of patients had resumption of cyclic bleeding and ovulation, with a good secretory endometrium.

According to Rock, the regimen described above should be employed for six months. An alternative method is Hamblen's schedule of cyclic therapy with Premarin and Pranone, which consists of 1.25 mg. of Premarin three times a day for 10 days followed by 1.25 mg. of Premarin and 10 mg. of Pranone three times a day for 10 days. If bleeding occurred during treatment, Hamblen discontinued the hormones for four to five days and then started another cycle of therapy.

Brown and associates[7] found that one large dose of estrogen administered on about the tenth day of the menstrual cycle may produce a sudden release of luteinizing hormone and consequent ovulation in cases of anovular menstruation. The giving of 2 mg. of Estinyl orally on the tenth day of the menstrual cycle has been thought to favor the release of the luteinizing hormone of the anterior lobe of the pituitary gland. As an alternative, 0.5 mg. of Estinyl could be given orally for five days starting on the fifth day of the cycle, for three cycles.

During normal pregnancy, production and excretion of estrogens gradually increases from the time of implantation of the ovum until shortly before labor begins. During the first part of the pregnancy the corpus luteum is the source of estrogens. Later the syncytial cells of the placenta elaborate estrogen. The activation of inactive estrogen takes place a week before labor, at which time it is freed in order to sensitize the myometrium for action of the posterior pituitary substances. Thus, in cases of threatened abortion, Vaux and Rakoff[8] suggested giving 1.66 mg. of Dimenformon benzoate or Progynon-B and 10 mg. of progesterone intramuscularly three times a week until the period of viability is reached. Smith's[9] schedule of dosage is based on the quantitative determination of hormonal levels throughout normal pregnancy. At the end of the sixth week of pregnancy, 5 mg. of stilbestrol is given daily by mouth as an initial dosage; this is increased by 5 mg. each week until the thirty-fifth week of pregnancy, when the drug is discontinued. Smith feels that estrogen given in this manner stimulates the patient's production of estrogen and progesterone.

Morton and Miller[10] have shown that estrogen given within the first 24 hours post partum in gradually decreasing doses is effective in suppressing lactation. I utilize stilbestrol for this purpose in the following dosage: 1 mg. four times a day for four days; 1 mg. three times a day for three days; 1 mg. twice a day for two days; and then 1 mg. each night for one week.

Spontaneous expulsion of a dead fetus may be hastened by giving large doses of estrogens[11] to increase the sensitiveness of the uterus. Dienestrol, 20 mg. five times a day for one week, has been of value in these cases. This treatment does not always succeed and, if not, the best therapy is watchful waiting.

Hypertrichosis associated with Fröhlich's syndrome reportedly has been improved by electrolysis followed by a six month course of therapy consisting of 1.0 mg. of dienestrol

orally three times a day for the first 10 to 12 days of the menstrual cycle. Thus, Hamblen and others have postulated that estrogen can be effective in preventing regrowth of facial hair. Such large doses may suppress menstruation temporarily and evoke episodes of metrorrhagia from a hyperplastic endometrium. I have not had any personal experience with the use of estrogens for hypertrichosis.

Although it is my practice to prescribe oral hormonal therapy for patients who have been subjected to a surgical menopause, some physicians resort to implantation of estrogen pellets. Zondek and Rozin[12] implant a 35 mg. pellet, and two and a half months later they implant another 35 or 15 mg. pellet. They recently suggested implanting the pellets in the posterior vaginal wall about 2 cm. beyond the vaginal orifice. A small incision is made in the vaginal mucosa and infiltrated with 0.5 per cent NOVOCAIN®; the wound is spread apart with a hemostat and the pellets are implanted. Implanting the pellets under the vaginal mucosa produced much greater activity than subcutaneous or intramuscular administration. The latter two routes may result in a fibrotic tissue reaction of sufficient degree to prevent absorption.

Some cases of migraine are thought to be due to hyperactivity of F.S.H.[13] For this purpose, I employ 0.1 mg. of dienestrol or 0.1 mg. of stilbestrol for 18 days following the last day of menstruation, repeating the course for at least four cycles.

Davis[14] has postulated that since the lack of estrogen causes atrophy of the postmenopausal vagina, administration of this hormone should cause thickening of the vaginal epithelium, better glycogen production, and subsequently a resistance to infection. Vaginal suppositories containing 0.5 mg. of diethylstilbestrol have been used, for one month periods. Premarin or dienestrol vaginal cream has proved quite effective in these cases of senile vaginitis. A saline douche a few hours before using the estrogenic agent rids the vagina of accumulated debris.

White and Hunt,[15] whose observations on pregnancy and diabetes have raised considerable controversy, advocate administering as much as 1.66 mg. of estradiol benzoate and 20 mg. of progesterone daily to pregnant diabetics, to aid both mother and baby. However, this treatment has not been universally accepted.

For treatment of the menopause, I prescribe dienestrol in the following dosage: 0.5 mg. every night for two months, 0.4 mg. for the third month, 0.3 mg. each night for the fourth month, 0.2 mg. for the fifth month, 0.1 mg. per night for two weeks, and finally 0.1 mg. every other night for two weeks. Active hormonal therapy for the menopause usually can be terminated in 6 to 12 months and should not be continued indefinitely.

I prefer dienestrol to Premarin for menopausal therapy because the latter often produces withdrawal bleeding. Also, dienestrol is more economical.

Natural estrogens are prescribed for patients with depression, memory impairment, insomnia, headache, tinnitus and psychoneurosis. Estinyl, Lynoral or Eticylol is used, in the following dosage: 0.05 mg. for two months, 0.04 mg. for the third month, 0.03 mg. for the fourth month, 0.02 mg. for the fifth month, and finally 0.01 mg. for two weeks and then 0.005 mg. for two weeks. If a natural estrogen is needed and the patient experiences nausea from one of these three drugs, one may prescribe Menformon in a dosage of 5000 I.U. each night for two months, 4000 I.U. each night for the third month, 3000 I.U. every night for the fourth month, 2000 I. U. each night for the fifth month, 1000 I.U. each night for the first two weeks of the sixth month, and 500 I.U. each night for the second two weeks. The gradual withdrawal of large doses of estrogen accomplishes a lasting cure for most patients with severe symptoms of the menopausal syndrome and prevents estrogen-withdrawal bleeding.

The administration of large doses of estrogen for treatment of the menopausal syndrome in a diabetic woman who is taking insulin may result in a reduction of the insulin requirement by at least one-third, as estrogen inhibits the diabetogenic hormone of the pituitary gland.[16]

Uterine bleeding that does not cease within

14 days after estrogen therapy is discontinued is an indication for a Papanicolaou smear, curettage of the endocervix and uterine cavity, and a cone biopsy of the squamocolumnar junction of the cervix.

Danziger[17] believes that estrogen therapy may have great value in properly selected cases of involution melancholia.

For menopausal osteoporosis, one may administer 2 mg. of dienestrol plus 10 mg. of buccal methyltestosterone or 1.66 mg. of estradiol benzoate in aqueous solution twice a week, plus 10 mg. of testosterone in aqueous solution twice a week intramuscularly. This is continued for a few months. Theoretically, osteoporosis is a decalcification due to inadequate amounts of estrogens and androgens. Thus, a protein depletion takes place which leads to a reduction of organic matrix of bone. Estrogen therapy in these cases should be supplemented by a high protein diet and vitamin C. Use of calcium and vitamin D should be avoided because estrogen or androgen therapy causes a decreased calcium and phosphorus excretion. The development of edema is an indication for use of ammonium chloride and a low salt diet.

Masters and Grody[18] recently reported on a small series of patients ranging in age from 64 to 89 years who received a combination of estrogens and androgens. All these women were at least 10 to 12 years post menopause. The most efficacious dosage and the one that produced the fewest side effects, such as withdrawal bleeding and endometrial hyperplasia, was 1 mg. of α-estradiol benzoate and 20 mg. of testosterone given intramuscularly twice a week. In order to eliminate the parenteral therapy, I would recommend the use of 1 mg. of dienestrol and 5 mg. of METANDREN® (Linguets) each night. Masters and Grody concluded that such hormone therapy for older women produced an elevation in physical, mental and emotional levels. They also felt that a rejuvenation of the cellular metabolism actually occurred, resulting in a reversal of the aging process. I hope that such therapy will be tried in larger series of cases, and perhaps in men also; we then can ascertain whether it should be utilized universally in aged persons.

There are innumerable other conditions in which estrogens have been employed, including carcinomatosis, mumps (prevention of mumps orchitis), strictures from lymphopathia venereum, and atrophic rhinitis. In some of these, estrogens have provided definite palliation, but in others their value is still questionable.

Perhaps the future will clarify some of the enigmas that still exist in this challenging link in the endocrinologic make-up of the female.

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Late Treatment of Burns

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THE treatment of burns is usually divided into two phases: (1) treatment of shock and (2) covering and healing of the wound. This latter phase has been done by the exposure method, the closed method, the open drainage method and, recently, the immediate excision of the burned areas and grafting in carefully selected cases.

The treatment of shock has received intensive study in recent years and considerable research is continuing in this field. Every effort is made to keep the patient alive so that he may later receive grafts to cover the defect. So much progress has been made in the treatment of shock that some day we may be confronted with a patient who has 80 or 90 per cent of his body burned, with full-thickness loss of skin, and no autogenous skin remaining to cover the wound. This certainly will present a problem to the surgeon, because homografts, as you know, are not successful, even though they are used in many cases as a skin dressing to tide the patient over critical periods. Considerable research is being carried out in an effort to find out why a homograft does not grow, but up to now the answer has not been found. So the dictum we must follow in the treatment of burns, after the shock has been controlled, is to get the area from which the full thickness of skin has been lost as clean as possible as soon as possible and to cover the defect with split-skin grafts. The salient principles and technical details are brought out in the cases illustrated in the accompanying photographs.

Closed Method

With the closed technic, the first dressing is not disturbed for 10 to 12 days, provided acute sepsis is not present. By this time the devitalized tissue generally is beginning to separate (figure 1). XEROFORM® incorporated

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FIGURE 1. First dressing on tenth postburn day. Slough about to separate.

FIGURE 2. Tubbing of burns facilitates removal of dressing and exudate, and physical therapy. Fine-mesh gauze still on legs.

in fine-mesh gauze is applied, and massive pressure dressings are changed daily so that separating slough and exudate can be removed. This is continued until the granulating areas are ready to receive the grafts.

Open Drainage Method

If a patient is seen relatively late after he has been burned, and if considerable exudate is present, there is no better way of improving the burned areas and preparing them for grafting than to tub the patient daily and apply wet dressings, which will promote drainage and bring the exudate to the surface (figure 2). Physical therapy to the joints, by encouraging motion during tubbing, is continually stressed. The layer of fine-mesh gauze on the burns is kicked off in the tub. Extensive burns are ready to receive grafts when the granulations are smooth, flat, shiny and painless. To obtain that type of smooth granulation which will receive a graft, a layer of fine-mesh gauze and pressure dressings must be used to prevent the granulations from growing into the interstices of the dressings and leaving little mushroomlike edematous masses which harbor bacteria and exudate. All personnel participating in changing of the dressings should wear sterile gloves and masks; the patient also should wear a mask.

Grafting Procedure

In using the dermatome to obtain split-thickness skin grafts, two very simple points are often neglected: (1) Most important, the blade must be sharp; (2) the drum must be dry so that the glue will stick. The thickness of the graft, of course, varies according to where it is to be placed. If the wound is badly infected, thin grafts will take better. The thicker the graft on an infected wound, the less likelihood that it will take.

The grafts applied to the burned area also require massive pressure dressings for stabilization and immobilization. The first dressing after extensive skin grafting of granulating wounds is best done in about three days. If any pustules have formed under the graft or if there is evidence of hematoma, these should

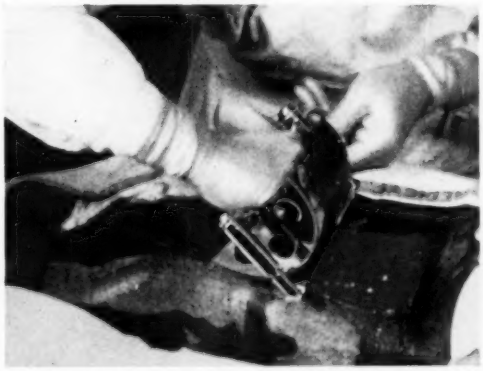

FIGURE 3. Removal of third crop of skin from same donor site. Note various depths of pigment of two previous donor sites.

be opened. This is important with relation to avoiding local infection, the principal threat to the success of skin grafting.

When extensive areas must be covered by skin grafts, it is possible to take two or three crops from the same areas of skin (figure 3). The greater the burned area that has already been covered, the greater the area of skin that can be taken (provided it is available) from the donor site. The patient is much better able to withstand secondary procedures because loss of proteins and blood from the burned areas already covered by skin grafts is under better control. Operating time can be reduced by using three or four drums, or even more, which are available and prepared with glue before the operation. It must be emphasized again that one must apply massive pressure dressings after these extensive applications of skin. Also, the donor site is pathologically similar to a second degree burn or partial-thickness loss of skin and must be treated as such. Xeroform pressure dressings are applied to the donor sites and left for at least 14 days, unless an acute infection develops. If dressings become loose, they are reinforced. These dressings should never be pulled off before the skin is entirely healed. If this is done, the new epithelium may be destroyed.

In the case of an eight year old boy who was first seen a considerable time after he was severely burned, homografts from the patient's mother were used (figure 4) because

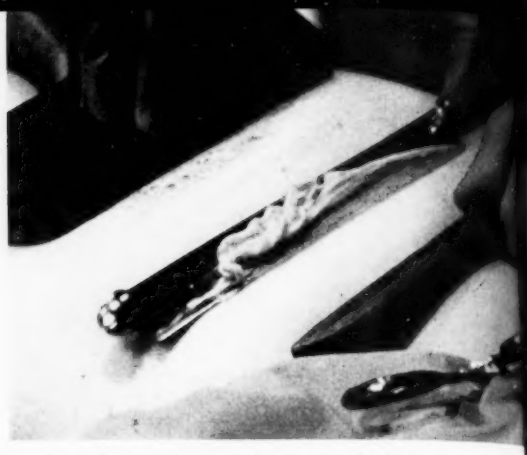

FIGURE 4. Cutting skin graft from mother's thigh.

not enough skin was available from the patient to cover the defect on his legs adequately. At the first operation, only two drums could be obtained from his back. Sheets of autogenous skin were applied around the knee joint to prevent contracture (figure 5). In taking skin from debilitated persons, saline may be injected into the depressed areas of the back to balloon them out so that the surface will be even and the drum can get hold of the skin without being obstructed by the bony prominences (figure 6).

Strips of skin were obtained from the thigh of the mother. (Such strips can be removed easily with a Weck or a Brown-Blair knife or an electric dermatome.) These were alternated with autogenous skin strips in covering the child's right leg (figure 7). The homografts were very thin, substituting merely as a skin dressing to dam back the proteins and thus

FIGURE 11. Well-demarcated third degree burn.

FIGURE 12. Posterolateral view of well-demarcated third degree burn.

FIGURE 13. Beginning excision of burn area.

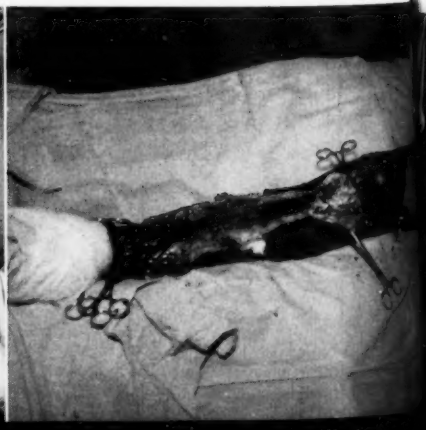

FIGURE 5. Granulating leg. Knee joint was grafted previously to prevent contracture.

FIGURE 6. Developing a smooth surface by injecting saline subcutaneously.

FIGURE 7. Alternate strips of autogenous and homogenous (marked with methylene blue) skin.

FIGURE 8. Homografts entirely covering right leg as a skin dressing.

FIGURE 9. Fourth postoperative day; all grafts have taken.

FIGURE 10. Both legs completely healed; replacement of homografts with scar epithelium.

FIGURE 14. Dissection of devitalized skin.

FIGURE 15. Leg prepared for grafts.

FIGURE 16. Fourth postoperative day; all graf have taken. Right leg was amputated becau of necrosis.

aiding in improving the general condition and in local healing of the autogenous strips. When alternate autogenous and homogenous skin strips are used, these do not have to be sutured; they are just laid on, and Xeroform pressure dressings are applied. In about four weeks the homografts begin to disappear, but meanwhile, if the patient's general condition is good, the autogenous skin will send out epithelium and fill in the area from which the homograft has disappeared.

Because of the paucity of autograft material, this child's right leg was entirely covered with the mother's homograft skin, used merely as a dressing to control loss of proteins and hemoglobin (figure 8). By the time this disappeared, the patient's condition had improved sufficiently so that autogenous skin could be taken from his abdomen and chest to replace the homograft. At the time the first dressings were removed, the mother's grafts were completely adherent and could not be pulled loose with a pair of thumb forceps (figure 9). Homografts usually remain from two to six weeks, sometimes as long as eight weeks. Figure 10 shows the end results in the case of this boy. The areas covered by grafts from the mother are covered by scar epithelium and are distinguishable from the autogenous skin grafts. This scar epithelium does not have all the properties of normal skin; i.e., it has no hair follicles, oil glands or sweat glands.

The case illustrated in figures 11 through 16 demonstrates the technic of immediate grafting. This procedure is still controversial but is gradually being more widely accepted. One of the most important objections is that it is difficult or impossible to tell immediately whether a third degree burn or full-thickness loss of skin has occurred. In this instance, however, it appeared that the area chosen for skin grafting was very well demarcated (figures 11 and 12). The patient had a combined electric and thermal burn. He hit a 20,000 volt wire which entered his right leg and ignited his trousers and burned an area on his elbow and on his skull. On the seventh day after the burn, the patient had recovered from shock. The devitalized area was excised (figures 13, 14 and 15) and prepared for reception of the grafts. As much skin as possible was obtained from the patient's chest and abdomen, but it was insufficient to cover the defect completely. Hence it was applied in strips. Homografts could have been applied between these strips, as in the case of the boy, but it was felt that the autogenous strips would be sufficient to fill in the uncovered portions. If this can be achieved, it is of course simpler than simultaneous use of homografts.

On the fourth postoperative day, the grafts had taken 100 per cent, and complete healing followed (figure 16). The other leg had to be amputated because it became completely necrotic from the electric burn; the tibia was exposed on the lateral surface from the ankle to the knee.

The results of successful skin-grafting procedures following extensive burns are extremely gratifying and more satisfactory when performed as early as possible after the injury. The principal causes of grafting failures are lack of proper preparation of the burned area, poor general condition of the patient, infection and lack of immobilization after the graft is applied.

Treatment of Congestive Heart-failure

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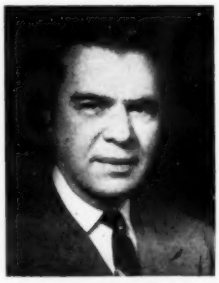

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THIS paper is an outgrowth of a symposium on the treatment of congestive heart-failure held at the annual meeting of the State Medical Society of Wisconsin. It is based on the question and answer discussion of the subject, with participation by general practitioners, internists and cardiologists with the aim of answering the basic problems in the treatment of a symptom complex which forms the bulk of everyday practice. No attempt, however, is made to cover every phase of a subject so voluminous and so controversial. The subject is limited to the discussion of failure associated with low cardiac output. No credits are given, but many of the facts and ideas presented herein are derived from the work of authorities in the field of cardiovascular disease.

William Withering's observations on digitalis in 1775, the revelation of the diuretic action of NOVASUROL® in 1919, and Schroeder and Schemm's popularization of the role of a sodium-poor diet, water and electrolytes in 1941 and 1942 constitute three milestones in the treatment of congestive heart-failure. Generally, however, the treatment of congestive heart-failure has not changed materially in the past 150 years since the introduction of digitalis. Rest, sedation, diet, digitalis and diuretics are used in very much the same way. Advances, however, have taken place in the increasing knowledge of the chemistry of the active principles of digitalis, new and better diuretics and the comprehensive role of food including salt, water and electrolyte metabolism, as well as our greater understanding of the body as a whole.

As the introduction of digitalis marked the beginning of cardiac therapy so does it continue to be the most effective agent in that

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therapy, since digitalis acts directly on the myocardium to restore compensation. All other measures are important adjuncts. In this realization lies the recognition that cardiac and extracardiac factors interact in the pathogenesis of heart-failure. Thus, effective treatment means digitalis and its adjuncts, rest, diet and diuretics.

Digitalis

Digitalis simply increases the force of systolic contraction of the heart muscle without alteration in the diastolic fiber size. This results in more complete ventricular emptying with a rise in output. The duration of systole is abbreviated, allowing greater time for ventricular filling and heart rest. The diastolic size of the heart is reduced, thus diminishing the oxygen expenditure for work output. The work capacity of the heart is thus increased and the over-all result is an increase in cardiac output and efficiency.

No fundamental difference has been found among the digitalis glycosides in their effect on the heart. Only the rapidity and degree of absorption, variability in potency and duration of action differ. For example, of the *purpurea* preparations, only 20 per cent of the digitalis leaf is absorbed in the gastrointestinal tract, while 100 per cent of the purified glycoside, DIGITOXIN,® is absorbed. Their duration of action is two to three weeks. The *lanata* extracts, DIGOXIN®, DIGILANID® and lanatoside C, have an oral absorptive range of about 20 per cent and their duration of action is two to seven days. The physician should consequently gauge the need of each individual in terms of absorption, potency and duration of action. It is experience with the precise drug which will allow manipulation of the digitalizing and maintenance dosage effectively without gross toxicity. This is the core of digitalis therapy.

The whole leaf remains the most widely used preparation. Usually, 1.2 to 1.5 gm. of the U.S.P. preparation given over a period of several days is an effective digitalizing dose range. About 0.1 to 0.2 gm. is excreted daily, and, consequently, this is the maintenance dose. Digitoxin has recently come into wide usage. It has uniform potency and it is equally effective when given orally, intramuscularly or intravenously. The digitalizing dose is 1.2 to 2.0 mg., and the maintenance dose is from 0.1 to 0.2 mg. It may be used in cases in which more rapid digitalization is needed and again, with experience, is a good drug to use for long-term digitalis therapy. Digoxin is also a purified glycoside derived from the leaves of *Digitalis lanata*. The intravenous digitalizing dose is 0.75 to 1.5 mg. The oral digitalizing dose is 2 to 6 mg. and maintenance dose is 0.25 to 0.75 mg. Rapid elimination has been cited as both an advantage and disadvantage of this drug. The answer is again the proper clinical usage. There are various other standardized and purified preparations such as URGININ® and ouabain which are rapidly acting substances for intravenous administration.

Rapid digitalization should be used only in emergencies such as rapidly progressing acute pulmonary edema. The usual decompensated cardiac has been on the way to decompensation for some time. A sudden electrolyte shift and disturbance in metabolic balance may result if too rapid digitalization is attempted. This electrolyte disturbance, which alters the calcium and potassium threshold of the myocardium to digitalis effect, in part explains the increased incidence of digitalis intoxication.

Rest

Rest lessens cardiac work and causes promotion of cardiac and renal efficiency and increased venous and lymphatic return from the lower extremities. Rest, however, does not always indicate complete immobility or maintenance of a specific position. Prolonged inactivity and hemoconcentration may cause muscular weakness, femoral phlebitis and subsequent pulmonary infarction. Rest means the limitation of exercise or activity to a degree necessary to promote and maintain cardiac efficiency, physical comfort and mental well-being.

Diuretics

The diuretics most frequently used are the mercurials, the acidifying salts and the xanthines. Carbonic anhydrase inhibitors are of more recent usage. The mercurial and xan-

thine diuretics act by reducing the reabsorption of the glomerular filtrate by interfering with the enzyme systems which normally effect the transfer of substances from the renal tubular lumen back into the blood stream. In addition to xanthine, diuretics cause increased glomerular filtration by improving renal blood flow. Acidifying diuretics usually act by mobilizing sodium from the interstitial fluids and body stores. Thus, sodium enters the circulation and is removed by the kidneys. The action of carbonic anhydrase inhibitors is to prevent tubular secretion of the hydrogen ion and the reabsorption of sodium.

The organic mercurial compounds are most efficient and quite nontoxic when combined with the xanthine theophylline in equivalent amounts. The theophylline causes faster and more complete absorption and increases the rate of urinary excretion of the mercury 100 to 300 per cent after intramuscular injection and 30 to 40 per cent after intravenous administration. The toxicity is also greatly reduced. MERCUHYDRIN®, SALYRGAN® theophylline, CUMERTILIN®, MERCUZANTHIN® and THIOMERIN® are the most frequently used mercurial diuretics. Thiomerin contains a mercaptan in place of theophylline. A solution of one of these diuretics usually is administered intravenously or intramuscularly in doses of 1 or 2 cc., but a solution of either Thiomerin or Mercuhydrin often is given subcutaneously. Their effectiveness is based on the experience of the physician in the usage of the particular diuretic and on his observation of the individual patient. Routine schedules without observation lead to undesirable effects such as dehydration and electrolyte depletion. Hypersensitivity reactions are rare, but I recently have observed such reactions in two patients. They were characterized by chills, fever and a rash occurring one to four hours after administration by the intramuscular route. These symptoms quickly subsided.

With the exception of Thiomerin, the same preparations listed above for parenteral use may be used orally. NEOHYDRIN®, another mercurial, is specifically a mercurial for oral use. However, the results have been inconsistent, and much juggling of dosage and close observation for untoward reactions such as nausea, vomiting, diarrhea, gingivitis and stomatitis are necessary. There are, however, some patients who will obtain satisfactory results with smaller and less frequent parenteral doses. Again, individualization is the keynote.

The answer to oral diuretic therapy may be the nonmercurials such as the carbonic anhydrase inhibitors—DIAMOX® and an amino metramide, MICTINE®, which is said to inhibit the resorption of sodium by the renal tubules. These products are of recent usage and need longer term study.

The theophylline compounds are the most useful of the xanthines because of their role in combination with organic mercurial salts as noted above. Theobromine and its compounds are still used for maintenance therapy, but are of low potency and doubtful effect.

Ammonium chloride, the most widely used of the acidifying salts, is a mild diuretic. It supplies the chloride ion which is essential for the maintenance of diuresis. Thus, it may be used by itself or as a potentiator of mercurial diuresis. The effective dose is 4 to 6 gm. and enteric-coated tablets are used to prevent gastrointestinal upsets. When used as a mercurial potentiator, ammonium chloride may be used continuously. When used as an independent acidifier and diuretic, interrupted use—four days off and four days on—is the preferred dosage.

Sodium-poor Diets

The use of sodium-poor diets and unfolding knowledge of electrolytes, water, and acid-base balance represent recent advances in the treatment of congestive heart-failure. A proper electrolyte balance along with restriction of salt to 3 to 4 gm. daily, as compared with the 6 to 15 gm. of salt in the average diet, and the administration of digitalis and ammonium chloride may keep a great many cardiacs compensated. The addition of a mercurial diuretic with the same dietary regimen may be indicated for the more handicapped patients. The severely congested patient may need a 200 mg. sodium diet to prevent piling up of sodium and the formation of edema fluid. The patient and his family should receive clear,

detailed instructions regarding these foods and their preparation, with attention to their palatability. They must know that mineral water and carbonated drinks contain sodium, as do the usual canned foods, unless specifically otherwise prepared. Crackers, biscuits, candy bars, antacids, cereals, etc. must be carefully screened. Salt-free bread and salt-free or sweet butter will reduce the sodium content by about 2 gm. The patient must determine the palatability of the various salt substitutes, and these should be used only after cooking, and then sparsely.

Caution, however, must be exercised since severe salt restriction and excessively induced diuresis may cause marked disturbance in body electrolytes. Salt depletion brings on the low-salt syndrome with its possible progression to azotemia and acidosis. Excessive loss of chlorides may carry off potassium and calcium and lead to alkalosis, renal failure and uremia. The possible acid-base disturbance along with unpalatability is the hindering factor in the use of ion exchange resins.

Fluid Intake

If the intake of sodium, the binder, remains within the range of the renal excretory capacity, water may be taken *ad lib.* An increase in the fluid intake above the 2000 to 3000 cc. range is indicated when there is associated renal incompetence with nitrogen retention. The rule should be unrestricted fluid to fit the need.

Comment

Much has been left unsaid and not all of the subject matter has been covered in this presentation. The psychosomatic approach, oxygen, sedation, anticoagulants and cortisone are all important, but were less in the tempo of the questioning and were not considered.

The endeavor has been to present the basic simple factors in the treatment of congestive heart-failure, and to recognize their inseparable actions as well as emphasize the importance of individualization of therapy and the hazards of overtreatment and undertreatment.

41st Annual

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Cleveland, Ohio, October 22-25, 1956

The Problem of Ulcerative Colitis

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Diagnosis and Treatment of Gynecologic Bleeding

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If the human uterus were an organ which never bled unless invaded by organic disease, our diagnostic problems would be infinitely simplified, but because the normal uterus is *expected* to bleed at certain times and under certain circumstances, more or less confusion is created whenever it performs this function in a disorderly manner—however slight the disruption of pattern may be. This confusion arises to a large extent from a lack of understanding, by both patient and physician, of the details of that physiologic phenomenon we call menstruation, and from an apparent unwillingness to try to distinguish menstruation from other likely causes of uterine bleeding.

Menstrual bleeding is regularly recurring bleeding, of limited duration, occurring from secretory (progestational) endometrium—that is, endometrium which has been influenced in a very specific fashion by both estrogens and progesterone. This form of bleeding nearly always is preceded or accompanied by characteristic symptoms (menstrual molimina), and for any woman it may be described in terms of quantity, color and consistency of discharge on the various days of the "period." The duration of flow rarely exceeds seven days and may, of course, be much shorter.

It is generally believed that menstrual bleeding does not reappear less than 19 or 20 days after the beginning of the previous episode, presumably because this represents the minimal time required for endometrial tissue to complete the changes peculiar to the proliferative, secretory and menstrual phases of the cycle. While the modal pattern for length of cycle is approximately 28 days, cycles as long as 35 days may be considered normal.

Causes of Bleeding

Having established menstruation as a phenomenon with specific boundaries, it is not

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difficult to recognize variations from the normal pattern, and to set menstruation apart from nonmenstrual bleedings which are not associated with regularly recurring shedding of secretory endometrium. A list of the more important menstrual abnormalities and nonmenstrual causes of uterine bleeding is shown in table 1. The various entities mentioned in the table are described adequately in modern textbooks, particularly those dealing with gynecologic pathology, and it will be assumed that the reader has some familiarity with these common lesions.

TABLE 1

COMMON CAUSES OF GYNECOLOGIC BLEEDING

I. Disturbances of menstruation
- A. Related to quantity and/or duration of bleeding
  1. Hypermenorrhea or menorrhagia (too much, too long)
     - a. Myoma uteri (especially submucous variety)
     - b. Irregular (delayed) shedding of endometrium
     - c. Endometrial polyp
     - d. Adenomyosis uteri
  2. Hypomenorrhea (scant and short flow) (no demonstrable organic lesions)
- B. Related to intervals between bleedings
  1. Polymenorrhea (cycles less than four weeks)
     - a. Basically short cycle
     - b. Premature interruption of cycle (various causes; often emotional basis)
  2. Oligomenorrhea (prolonged cycles)
     - a. Delayed ovulation (?)
     - b. Persistent corpus luteum (?)

II. Nonmenstrual bleedings
- A. With an estrogenic basis
  1. Hyperplasia of the endometrium
  2. Bleeding after use of estrogens
  3. Bleeding from hypoestrogenic, anovulatory endometrium
  4. Bleeding with estrogen-producing tumors of ovary
  5. Ovulation bleeding
  6. Bleeding from atrophic (senile) endometrium
  7. Bleeding from senile vaginitis
- B. Associated with miscellaneous lesions (with or without interposed menstrual bleedings)
  1. Disturbed pregnancy (abortion, ectopic)
  2. Carcinoma (vagina, cervix, corpus, tube)
  3. Polypoid lesions
     - a. Cervical polyp
     - b. Pedunculate submucous myoma
  4. Endometrial infections (especially tuberculosis)
  5. Vaginal trauma (mechanical, chemical)

Making the Diagnosis

History—A carefully dated and thoroughly reliable account of the patient's story is without question the most important feature of diagnosis. Details are essential, and these must be put together into a chronologic account relating the current problem to the patient's previous experiences with uterine bleeding. If such information is not immediately available, and if the problem is not one involving the prompt control of alarming loss of blood, it is best to accumulate the necessary historical data by direct observation over whatever period of time may be dictated by circumstances. Not infrequently the complaint fades into insignificance as it is scrutinized day by day and as the minutiae of the situation are recorded. Commonly the episode in question has just about run its course and is destined not to recur, so that mere watchful expectancy will bring about the desired result—cessation of the abnormal bleeding and restoration of a normal menstrual pattern.

Examination—Pelvic examination should be done while the bleeding is visible; otherwise one finds himself in the strange position of attempting to treat something which he has not observed. If the patient comes for her initial visit in a nonbleeding phase, arrangements must be made to see and examine her again as soon as possible after the bleeding resumes.

In addition to the usual speculum visualization of vagina and cervix, and bimanual rectovaginal (never vaginal alone) palpation, it is helpful often to determine the total length of the uterine cavity with a graduated sound. Not uncommonly the first pelvic examination is grossly misleading because of abdominal rigidity, full colon or full bladder, and one

should never be overly positive about the presence of pelvic masses on the basis of a single examination.

A goodly number of the bleeding problems may be disposed of solely on the basis of history and examination, most particularly those related to timing of the flow, and certain of the nonmenstrual disturbances. But when the problem is one of profuse or prolonged bleeding, then an explanation within the uterine cavity must be sought despite normal gross anatomic findings.

Endometrial biopsy, as an office technic, has been of limited usefulness in my experience. If it produces adenocarcinomatous tissue, for example, in a postmenopausal woman with a typical story of carcinoma of the uterine body, obviously it has furnished the diagnostic answer rather simply. On the other hand, a fragment of essentially normal endometrium obtained with a biopsy curet represents only the small area of endometrial surface sampled by the curet and reveals nothing about potential lesions in adjacent areas. Frequently the specimen consists largely of blood and mucus, with fragmented bits of glandular tissue interspersed, and cannot possibly lead to any worthwhile conclusion. Complete curettage of the uterine cavity not only provides adequate tissue for diagnosis but also affords an opportunity to examine the pelvic organs when the patient is anesthetized —often a very revealing procedure. Curettage has the additional advantage, in some instances, of being a therapeutic as well as a diagnostic device.

Curettage of the uterus—When history and physical examination have not provided a completely satisfactory answer as to the cause of bleeding, curettage is the next logical step. This is especially to be recommended when dealing with episodes of bleeding which are too profuse and too prolonged, or merely prolonged but lacking the element of profuseness. While curettage is a minor operation requiring no special preparation of the patient beyond a preanesthetic period of fasting, satisfactory results are achieved only through rigid adherence to a few simple rules.

In the first place, curettage must be done at a time when the tissue is likely to demonstrate the diagnostic features one hopes to find. This is absolutely essential in looking for irregular shedding of the endometrium, which may be found only during the bleeding phase of the cycle and well beyond the time when normal desquamation is complete (hence the necessity of curetting five or six days after the onset of flow). Where the major diagnostic possibility is endometrial hyperplasia or one of the other anovulatory varieties of bleeding, it is desirable to curet as soon as possible after the onset of bleeding so that there will be ample superficial endometrium for diagnostic purposes.

Attention to details in performing the operation may be very rewarding. An effort should be made to remove lengthy strips of endometrial tissue and to search for elusive polyps with a small grasping instrument (such as the Randall kidney stone clamp recommended by Scott). The tissue is collected on moist strips of gauze lying along the posterior vaginal wall and tucked in behind the cervix. Several of these are used if necessary, depending on the amount of tissue and blood, each strip being carefully rolled up and set aside for subsequent inspection. When the operation is over, and when all possible information has been obtained through bimanual examination of the anesthetized patient, then the surgeon must leisurely view the curettings under a good light and place the clean fragments of tissue (no clotted blood attached) in a bottle containing a suitable fixative solution. Polyps, or fragments suspected of being polyps, should be bottled separately lest they be lost in the total mass and escape sectioning. Similarly, material removed initially from the endocervix must be kept separate from endometrial tissue when one is attempting to localize the site of a carcinoma. Finally, he must attach to the specimen an accurate summary of the historical data, without which it may be impossible for the pathologist to return anything resembling a sensible and helpful diagnosis.

Pathologic examination—If the operator is not capable of acting as his own pathologist, he must ally himself with a pathologist who has an enthusiasm for endometrial tissues,

who knows the intricacies of utero-ovarian physiology, and who is willing to take whatever time and pains may be necessary to reach a conclusion compatible with the facts at hand. Such a pathologist will, of course, be intolerant of inferior technic in the preparation of tissue sections and will have the patience and perseverance to search, when necessary, for additional evidence buried in the paraffin block or in the residual gross material. There is never any real urgency about making the final diagnosis instantly from curettings, and with rare exceptions the information obtained from rapidly prepared frozen sections of endometrium is quite unsatisfactory. Excellent permanent sections of all available tissue can be made within 6 to 12 hours whenever the patient's problem demands a prompt answer.

Decisions Regarding Treatment

History and examination alone will dispose of those patients with no gross abnormalities and with minor complaints perfectly compatible with good health. In this category I would put most of the disturbances of menstrual timing, as well as bleeding at the time of ovulation, and hypomenorrhea. There are no specific therapies for these problems and they are best handled by a program of interested watchful expectancy, with periodic examination and reporting of details accumulated in the interim between visits.

Another rather small group of patients may be disposed of by major surgical treatment as soon as feasible following the initial office examination. These are women whose bleedings are associated with large uterine or adnexal masses which will require operative removal in any event, and whose ages are such that ovarian preservation is not a major concern. But even in the case of a rather obvious mass, when abnormal bleeding is an associated problem there is much to be said in favor of a preliminary curettage. Occasionally, examination of the anesthetized patient reveals a *smaller* myomatous mass than had been thought to exist. If the cavity is not unduly distorted and if the bleeding is associated with a polyp, or irregular shedding, or hyperplasia, there may be gratifying improvement after curettage alone, and hysterectomy may be postponed. Occasionally one finds an endometrial carcinoma or sarcoma when it has not been anticipated seriously, and further therapy then may be planned more effectively and with somewhat greater expectation of a favorable result.

A third small group is made up of those patients in whom the correct diagnosis will be rather obvious after the initial study and who, unlike the first group, will require some sort of specific therapy, usually short of laparotomy, to correct an organic lesion. In this category I include pedunculate myomas and polyps extending through the external cervical os, some of the carcinomas (gross vaginal and cervical lesions), vaginal trauma (physical or chemical) and some of the disturbed pregnancies. The treatment of many of these problems will include curettage, of course, but largely as a therapeutic device to rid the patient of an already obvious source of bleeding.

This leaves us with a large residue of patients who have no striking physical findings but whose histories indicate that something should be done reasonably soon to eliminate excessive or prolonged bleeding, or to eliminate (or establish) an association between the bleeding in question and a malignant process in the generative tract. Curettage is essential for these women; in many cases it may be therapeutic as well as diagnostic.

Patients who are candidates for prompt curettage are those with hypermenorrhea, those with irregular bleeding presumably on an estrogenic basis, and those with bleeding after the menopause. Women with cyclic hypermenorrhea (regularly recurring episodes of menorrhagia) should be curetted five to seven days after the onset of bleeding, since only then can irregular shedding of the endometrium be demonstrated; the other hypermenorrheic lesions may be found with equal facility at this time in the cycle. In women without cyclic patterns of bleeding, curettage may be done at any time, but preferably at the very onset of an episode of bleeding in order that the endometrial layer may be observed in its full thickness. Those with postmenopausal bleeding should be curetted

promptly. Rarely, in situations where exogenous estrogens have been administered for considerable periods of time, one may be justified in postponing curettage for not more than a week or two in order to test the effect of simply withdrawing estrogens.

Treatment After Curettage

Only in the few instances when carcinoma of the endometrium or endocervix is found is it necessary to undertake further treatment at once. To this group one might add the occasional patient with an ovarian neoplasm which was not detected by the preliminary examination but which became obvious during examination under anesthesia.

For virtually all others there may be a period of waiting to determine whether the curettage was beneficial, and this decision is made on the basis of careful scrutiny of the next few episodes of bleeding. Ordinarily, curettement of the endometrium does not change the ovarian cycle and subsequent menstruation will appear at the expected time with reference to the previous period. Removal of endometrium during the secretory phase of the cycle is likely to result in hypomenorrhea because of a relative lack of endometrial tissue, and in such cases one must wait for the second episode of bleeding after the curettage to assess the true situation.

The therapeutic effects of curettement are most striking with irregular shedding of the endometrium, endometrial polyp, small myomatous uterus without gross distortion of the cavity, postmenopausal bleeding not associated with carcinoma, and retention of gestational elements.

Failure to control menorrhagia of a serious degree usually is an indication for hysterectomy, particularly if there is no desire to preserve the uterus for reproductive purposes. In the menopausal woman, however, one may consider irradiation of the ovaries as a means of abolishing uterine bleeding if for any reason the surgical approach seems undesirable.

Despite the numerous recommendations of hormonal therapy for virtually every sort of uterine bleeding disturbance, it is thoroughly reliable in only one situation—hyperplasia of the endometrium. When this diagnosis is made by curettage, and when the goal is establishment of regular ovulatory cycles, progesterone is given 21 to 24 days after the curettement. This is repeated at intervals of precisely four weeks on three or four occasions. A single injection of 50 or 100 mg. appears to be just as effective as divided doses given over a period of four to five days, as some have advised. Menstrual-like bleeding occurs four to six days after the progesterone is given, and eventually, for reasons that are obscure, normal menstrual cycles resume and persist without further therapy. While this treatment is obviously best suited for the young woman, it may be applied at the menopausal age if one chooses to perpetuate uterine function until estrogenic activity in the ovaries falls below an effective level.

While estrogenic hormones may be helpful initially in the control of some forms of acute uterine bleeding, cessation of therapy is followed very often by recurrence of the bleeding. Such an undesirable effect may possibly be avoided by gradual diminution of dosage over a period of three weeks, with prompt resumption of higher doses if estrogen-withdrawal bleeding should appear despite efforts to prevent it. Estrogen given intravenously has been recommended for prompt control of bleeding, but the necessity of giving it every 6 to 12 hours until bleeding ceases makes it somewhat impractical for those patients who are not hospitalized. In the final analysis this sort of stopgap approach to the problem merely postpones for some the day when a definitive diagnosis will be made by curettage. For others, the hormonal therapy probably is quite unnecessary since most of the individual episodes of bleeding terminate spontaneously if allowed to do so. Rarely, if ever, will bleeding which is so profuse as to be considered a medical emergency respond to the empiric administration of either estrogenic or other types of hormones.

Success in managing abnormal uterine bleeding lies in making a correct diagnosis of its cause. By careful correlation of history, gross examination of the pelvis, and histologic details one should be able to reach definitive

diagnoses in well over 90 per cent of patients. With a diagnosis at hand, specific therapy may be instituted intelligently if and when indicated. The indiscriminate use of hormones or any other pharmaceutical agents is unwise, unnecessary and frequently harmful.

Case Reports

The following synopses of case histories are presented to illustrate certain types of problems encountered and the solutions which were worked out.

Case 1—A 27 year old single white woman first seen by me on February 19, 1954 complained of two episodes of profuse and prolonged vaginal bleeding which were spaced abnormally with reference to her previous menstrual pattern (cycle length four weeks, duration of flow six days). The last normal menstruation had begun December 18, 1953 and had been associated with her usual degree of dysmenorrhea. On January 6, 1954, crampy pelvic pain developed. She was examined elsewhere by a gynecologist three days later, and was advised to submit to exploratory laparotomy because of the possibility of "internal bleeding." The following day she began to bleed, somewhat prematurely, on the twenty-fourth day of her cycle, and this bleeding persisted for 10 days. When the flow had ceased she was re-examined by the same physician and operation was advised again. On January 30, just three weeks after the onset of the previous flow, she started to bleed again and continued for 20 days, passing numerous large clots and experiencing much crampy pain, despite a "shot" given on February 11 "to stop the flow." When examined on February 19 she had just stopped bleeding and bimanual examination disclosed only slight enlargement of the uterus and the right ovary. A detailed history brought out the fact that she might have become pregnant on several occasions in November or December; thus it seemed that the most likely diagnosis was incomplete abortion. Watchful waiting was advised.

Further bleeding, alternately heavy and light, occurred from March 7 through March 17, and it resumed again on March 31. Since the bleeding was still in progress 10 days later, curettage was done. A large amount of tissue was recovered from the upper posterior uterine wall and this showed findings consistent with subinvolution of the placental site. Thirty-one days later a normal menstrual period started and lasted for five days. The patient has been followed regularly for more than a year since the curettage, has continued to have normal menses at intervals of 24 to 28 days, and has had no obvious gross abnormalities of the generative organs.

Case 2—A 48 year old married woman first seen on September 30, 1947 was complaining of prolonged and profuse vaginal bleeding. Her last normal period had occurred in April 1947. She was amenorrheic during May, June and July, but had been bleeding continuously since August 16 (more than six weeks). Two other physicians had prescribed oxytocics and stilbestrol, the latter seeming to make the bleeding worse. Curettage on October 1 revealed endometrial hyperplasia and was effective in stopping the flow. The patient was told to report any further bleeding at once, but she failed to mention until November of the next year that she had been bleeding intermittently since August 1948. Endometrial biopsy demonstrated a recurrence of the hyperplasia and, because the patient was fearful of surgical therapy but wished to be free from bleeding, it was decided to terminate ovarian function with x-rays. In four treatments as an outpatient, 680 r was delivered to the ovaries. Spotty bleeding persisted for 30 days, but during the last six and one-half years there has been no recurrence and semiannual pelvic examinations have shown no abnormalities of any kind.

Case 3—A youthful-appearing woman, 52 years old, consulted me on April 9, 1954 because she had begun to bleed moderately the day before, only 12 days after the onset of what had seemed to be a normal period lasting the usual five days. Menses had begun at age 12, cycles were 21 to 26 days in length, and there had been one term pregnancy 15 years previously. There was a small amount of old blood in the vagina and the uterus had an irregular contour resulting from a myoma,

about 5 cm. in diameter, in the left cornual area. Since the bleeding was not excessive, watchful waiting was advised. The bleeding became more profuse the next day, but stopped within 48 hours after the initial examination. During the next nine months menses appeared at intervals of 20 to 30 days. While discussing the onset of her bleeding in January 1955, the patient's casual remark that her menstrual period would prevent a short week-end trip indicated that she had withheld information about the profuseness of flow in recent months. She had been afraid to leave home while bleeding because at times even two pads worn at once were inadequate.

Curettage was done two days later, revealing menstruating endometrium and a uterine cavity stretched out to a total length of almost 12 cm. The cavity was distorted by a submucous myoma on the upper posterior wall, and the previously noted subserous tumor had enlarged somewhat. When the patient was told that a myomatous uterus of this sort was likely to produce further menorrhagic episodes, she elected to waive the usual period of watchful expectancy and demanded immediate removal of the uterus, feeling that she would dread the prospect of hospitalization at some future date. Hysterectomy was done two days later, and the uterus contained numerous small myomas, three of which were protruding to various degrees into the endometrial cavity, thus accounting for the progressive menorrhagia.

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Management of the Pregnant Diabetic Patient in a Private General Hospital

A 10 YEAR STUDY

ROBERT A. JOHNSTON AND DOYE R. BRIDGES*

The University of Texas Postgraduate School of Medicine, Houston

THE complication of pregnancy in diabetes mellitus has become more frequent since the advent of insulin in 1921. Some authors now believe that the properly treated diabetic woman has approximately the same rate of fertility as the nondiabetic.[1] We must meet the increased incidence of pregnancy among diabetic women with greater awareness of the many peculiarities concerning management of these cases. Various authorities have outlined satisfactory methods but there is by no means complete agreement among the profession.

We shall present the results of a study of all viable pregnancies in diabetic women delivered at St. Joseph's Hospital in Houston from 1944 to 1954. These cases are from the records of both private and clinic practices and both specialists and nonspecialists. Methods of management have varied, as have the results. While the results may not be exceptional, we believe much can be learned from them, particularly with regard to management of the pregnant diabetic patient.

Material

During the decade covered by this series, 61 pregnant diabetic women were admitted to St. Joseph's Hospital. Three were delivered elsewhere and four had abortions prior to 28 weeks' gestation (13, 18, 26 and 26 weeks), leaving a total of 54 deliveries after the twenty-eighth week of pregnancy. These 54 cases comprised the material for our study.

ROBERT A. JOHNSTON

DOYE R. BRIDGES

The total viable deliveries during this 10 year period numbered 61,291, making the incidence of diabetes in our series 1 in 1,135.

We classified the 54 pregnancies (41 patients) according to the system outlined by White.[2] We favor this method of classification because it is the most frequently used, and its practical application generally is very satisfactory. Since x-rays of the pelvic vessels were not available in most of these cases, and in only one patient was there coexistent early

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TABLE 1

CLASSIFICATION OF DIABETIC PREGNANCIES*

CLASS	SEVERITY	NUMBER OF PATIENTS	PER CENT
A	Requiring no insulin and little dietary regulation	5	9.3
B	Onset after age 20 years; duration less than 10 years	23	42.6
C	Onset between 10 and 19 years of age; duration between 10 and 19 years	20	37.0
D	Onset before age 10 years; duration 20 years or more	6	11.1

*Based on system outlined by White.[2]

nephritis, we placed our patients only in classes A, B, C and D (table 1). This classification seemed to be more stable as a patient progressed from one pregnancy to another than the classification based on insulin dosage. The latter method was especially misleading if the patient was much overweight. One of our patients, for example, required 80 units of insulin daily during her first pregnancy, whereas during a later pregnancy, following a 20 lb. weight reduction, she was controlled on diet alone.

A review of the obstetric histories of the 41 patients proved rather interesting and appears in table 2. More than one-third of the 121 pregnancies occurred before clinical diabetes developed. We must conclude that any pregnancy in a diabetic woman or even one with preclinical diabetes very likely will result in failure unless the patient receives the very best diabetic and obstetric management.

TABLE 2

OBSTETRIC HISTORIES OF 41 DIABETIC MOTHERS

Total number of pregnancies	121
Present number of living children	73
Abortions	17
Stillbirths	22
Neonatal deaths	5
Premature deliveries	15
Later deaths	4
Abortion rate, 14.0 per cent	
Fetal mortality rate of viable pregnancies, 26.0 per cent	
Total fetal and neonatal mortality rate, 36.4 per cent	

A history of several late abortions, stillbirths or extremely large infants should make one suspect preclinical diabetes and be alert for its complications.

Fetal Mortality

Eastman[3] has stated that "almost all maternal deaths today from diabetes complicated by pregnancy are due to neglect." The standard accepted today for evaluating obstetric management of diabetic patients is the fetal mortality rate. The fetal deaths in our series are summarized in table 3. The 22.2 per cent mortality rate includes all deaths of infants

TABLE 3

FETAL MORTALITY IN 54 DIABETIC PREGNANCIES

CLASS	DELIVERED	DEATHS	MORTALITY RATE
A	5	1	20.0%
B	23	5	21.7%
C	20	4	20%
D	6	2	33.3%
	54	12	22.2%

TABLE 4

FETAL MORTALITY ACCORDING TO PRACTICE OF ATTENDING PHYSICIANS

TYPE OF PRACTICE	NUMBER DELIVERED	DEATHS	MORTALITY RATE
Specialist	29	4	13.8%
Clinic	10	2*	20%
Nonspecialist	15	6	40%

*Includes one infant with spina bifida and hydrocephalus.

who reached viability in both the antepartum and neonatal periods and is comparable with that in many large series. It does not, however, compare favorably with many of the better controlled series. This is probably because many of the physicians who delivered diabetic patients in this hospital may have had little experience with this entity. Table 4 may help to illustrate this point.

Prenatal Care

Eastman also has stated that the main objective of management of the pregnant diabetic is rigid control of the disease,[3] and this requires close supervision by a competent internist. In 42 of our cases an experienced internist was consulted during the prenatal period and in 12 cases the diabetic control was directed by the attending accoucheur alone. The fetal loss in the former group was 14.3 per cent, and in the latter, 50 per cent. These figures should make clear the value of teamwork in managing these cases.

Excellent methods for prenatal management of the diabetic have been described by Eastman,[3] Douglas and associates,[4] Pedowitz and Shlevin,[5] White[2] and others, and we therefore will not present an outline here. We do wish, however, to stress a few points which we consider helpful.

Having the diabetic patient near her ideal calculated weight before the pregnancy begins constitutes one of the greatest advantages in prenatal care, because radical weight changes even during early pregnancy often predispose to poor diabetic control. The overweight patient without weight reduction, on the other hand, is difficult to manage and requires much larger doses of insulin. In the obese patient, therefore, weight reduction should be cautiously but certainly undertaken.

Careful weekly observation of the pregnant diabetic woman affords an opportunity for the earliest possible detection of the many complications that may develop, e.g., acidosis, toxemia, polyhydramnion, pyelitis and other infections. Failure to control any of these as rapidly as possible may place the fetus in jeopardy. One must be especially careful not to depend on urine sugar determinations alone as evidence of diabetic control, since lowered renal thresholds and lactosuria may make this test somewhat undependable. Frequent determination of blood sugar, daily measurement of urine acetone and close attention to clinical symptoms of acidosis and insulin reactions must be the primary regulating factors.

We employed the hormone therapy advocated by White in only one case in this series. We are awaiting the results of further investigation before advocating its use.

Complications

Besides rigid control of the diabetes, prenatal care of the pregnant diabetic woman consists primarily of early detection and control of the many complications which may develop. Table 5 lists the complications encountered in our series, as well as fetal mortality accompanying each complication.

Preeclampsia developed most frequently, in 31.5 per cent of the pregnancies. The fetal

TABLE 5

COMPLICATIONS IN 54 DIABETIC PREGNANCIES

COMPLICATION	NUMBER OF CASES	FREQUENCY	FETAL DEATHS	FETAL MORTALITY RATE
Hypertension only	8	14.8%	1	12.5%
Albuminuria only	6	11.1%	0	
Preeclampsia	17	31.5%	5	29.4%
Polyhydramnion	15	27.8%	6	40%
Acidosis	14	25.9%	6	44.4%
Placenta praevia	1	1.9%	0	

mortality of 29.4 per cent for this group would be much higher if we excluded many very mild and quickly controlled instances of preeclampsia in which the fetal salvage rate was very good. It seems to us now that if a pregnancy has reached the thirty-fourth week and a definite diagnosis of preeclampsia is made, the patient should be stabilized carefully from both diabetic and toxemic viewpoints and then delivered by the most suitable method. If a patient has not reached the thirty-second week of gestation one must be more conservative, since the fetal mortality rate from prematurity will exceed 30 per cent.[6] Between the thirty-second and thirty-fourth weeks of gestation one must individualize each case carefully as to suitability of cervix, size of infant and patient's general condition.

Polyhydramnion occurred much more frequently among our patients than in other reported series.[3-5,7] It seems probable, therefore, that our records include many mild and even questionable cases of this condition. The accompanying fetal loss of 40 per cent, however, does seem to indicate its seriousness. We feel that these pregnancies should be terminated according to the outline presented for preeclampsia if x-rays do not reveal serious fetal abnormalities and the fetal heart tones are good. The only difficulty with this plan is that apparently polyhydramnion often is associated with fetal distress and the diagnosis is questionable until it is too late to save the infant. The withdrawal of amniotic fluid through an abdominal puncture has been advocated and is without great risk, but it seems unnecessary except in rare cases.

Acidosis developed in 25.9 per cent of our cases, with an accompanying fetal mortality of 44.4 per cent. There can be no doubt that this complication results in many fetal deaths and that its early detection and treatment are essential. If control of the diabetes becomes too difficult after the pregnancy reaches the thirty-four week, the fetus probably will find an incubator more satisfactory than the womb of an acidotic mother.

Therapeutic Abortion

Because St. Joseph's Hospital is a Roman Catholic institution, there were no therapeutic abortions in this series. We have, however, observed the successful termination of pregnancies in many cases of women with previous obstetric failures who would have had therapeutic abortion recommended elsewhere. One patient in this series had a successful pregnancy following four macerated stillbirths. Another patient with nephritis has had two successful pregnancies subsequent to delivery of a macerated stillbirth reported in this series, and so far as we can determine has not had an increase in the severity of her disease as a result. Most of the patients in this series were contacted when this report was prepared, and it is our opinion that there have been no permanent ill effects or increased severity of the disease as a result of pregnancy. On this basis we believe that therapeutic abortion is rarely, if ever, indicated in pregnant diabetic women.

Time of Delivery

The time chosen for delivery of the diabetic patient almost always should depend on what is best for the infant. The severity of the disease, ease of control, size of the fetus and development of complications are the primary considerations in determining the optimal time for delivering a live infant with the best chance for extra-uterine life.

Two infants were delivered following spontaneous premature labor prior to the thirty-second week of gestation (table 6). One of these was stillborn and the other died seven hours after delivery. Between the thirty-second and thirty-seventh weeks of gestation, nine patients went into spontaneous labor. Labor was induced in five, and 17 were delivered by cesarean section. One of these infants had died in utero at 33 weeks and one died of pulmonary atelectasis shortly after delivery. Labor had been induced at 34 weeks because of polyhydramnion in the latter case. There were 21 infants delivered after the thirty-seventh week of gestation, four by cesarean section. Six were macerated stillbirths, having died in utero at 36, 37, 39 and three at 40 weeks. One infant died during a difficult mid-forceps delivery and one died 26 days post

TABLE 6

FETAL MORTALITY BASED ON TIME OF DELIVERY

TIME OF DELIVERY	TOTAL DELIVERED	VIABLE INFANTS	PREMATURE INFANTS	STILLBORN INFANTS	NEONATAL DEATHS	TOTAL FETAL MORTALITY
28-32 weeks	2	0	2	1	1	100%
32-37 weeks	31	29	3	1	1	6.5%
37-42 weeks	21	13	0	7	1	38.1%

partum of spina bifida and hydrocephalus.

In analyzing the results in these 54 pregnancies, certain factors which will help us lower our fetal mortality become evident. We know that better control of the diabetes and better care of the premature infant will reduce fetal deaths occurring between the twenty-eighth and thirty-second weeks. The group delivered between the thirty-second and thirty-seventh weeks seem by far the most fortunate. One of these deaths was completely unexplained, having occurred at 33 weeks' gestation in an apparently well-controlled class B patient. The second was a neonatal death which may have been due to inadequate pediatric care. It is in the group delivered between the thirty-seventh and forty-second weeks that the greatest improvement in fetal mortality appears possible. All but one, or possibly two, of these eight deaths might have been prevented by early elective delivery. Jones[8] stated that he sees no advantage in early delivery of the diabetic patient, but at the same time he reported that 59 per cent of the fetal deaths in his series occurred after 36 weeks' gestation. We believe that each case should be individualized but that, in general, all patients in classes C, D, E and F should be delivered electively at 35 to 36 weeks' gestation if the fetus seems to be 6 lb. or more in size. All patients in classes A and B should be delivered at this time if there is any evidence of toxemia, acidosis or polyhydramnion, or any time the fetus seems to be of excessive size.

Miscalculation of the estimated date of confinement is still an unsolved problem, and one fetal death in this series probably could be attributed to it. If one is to deliver most diabetic patients electively at 35 to 36 weeks' gestation, extreme care must be taken that the infant is not too small. At this point we would like to stress again, however, that the danger of intra-uterine death after 36 weeks is far greater than the danger of death due to prematurity. The menstrual history, quickening, prenatal record of fetal growth and impression of fetal size by abdominal and vaginal examination should all be correlated carefully to determine the stage of gestation. X-rays of the fetal skeleton as described by Adams et al.[6,7] also aid greatly and should be made routinely, but at the same time one cannot wait for the development of calcification in the distal femoral epiphysis in the severe or uncontrolled diabetic or in cases where clinical judgment tells one that the fetus is of average size. After the thirty-sixth week of gestation the placenta can be considered postmature.

Method of Delivery

Once the optimal time of delivery is established, the patient should be admitted to the hospital early enough to allow careful evaluation and stabilization of the diabetes. She should be changed to unmodified insulin 24 to 48 hours before the onset of parturition or abdominal delivery. The pelvis, fetal size and position, condition of cervix and station of the presenting part should be carefully evaluated, and if induction is possible without increased fetal risk, this should be done with PITOCIN® or amniotomy or both.

It is needless to state that if delivery is advisable prior to 37 weeks' gestation, most cases will not be favorable for vaginal delivery by induction of labor because of an unripe cervix. In these cases there should be no compromise; cesarean section should be performed.

In this series there were 21 cesarean sections for an incidence of 39.9 per cent. Five of these were performed for obstetric indications and 16 were elective early sections. All cases were reviewed carefully according to the criteria already set forth, and the optimal time for delivery was determined. If cesarean sections were necessary in all the additional cases requiring delivery prior to the thirty-seventh week of gestation, our cesarean section rate would have been raised from 39.9 per cent to 57.4 per cent. Our over-all fetal mortality would have been lowered from 22.2 per cent to 9.3 per cent. If we may be allowed to speculate on our "hindsight," we should have saved seven infants by performing 10 additional cesarean sections.

Care of the Newborn

We are indebted to the recovery and premature nursery staff of St. Joseph's Hospital and to many excellent pediatricians for the survival of many of the infants in this series. Only one infant's death may have been attributed to inadequate pediatric care, whereas 18 of the surviving live babies had moderate to severe difficulty at some time during the early neonatal period. Although blood sugar levels were obtained on many of these infants, there was no evidence that hypoglycemia was responsible for their distress. Two infants had congenital anomalies, one spina bifida and hydrocephalus, another hypospadias and undescended testes.

The infants in this series were managed by various routines, but the following method seems to be very satisfactory: Immediately after delivery, the upper air passages should be carefully aspirated and the stomach emptied. The infant is then positioned for postural drainage in a previously heated incubator and oxygen and moisture are supplied for the first few days. Antibiotics are employed early if indicated and fluids withheld long enough to allow dehydration in the edematous infant. All these infants should be treated as prematures and receive the utmost care and observation.

Choice of Anesthetic

Since the babies of diabetic mothers are treated as prematures, it seems logical to employ the same concept in selecting any analgesics and in choosing an anesthetic at the time of delivery. A well-trained and cooperative anesthetist should be considered an important member of the team along with the internist, obstetrician and pediatrician. Each case must be individualized and as little anesthetic given as necessary to effect a safe delivery. Pudendal block or local infiltration, when possible, offers the least hazard to the infant.

Summary

1. We have presented a critical survey of 54 deliveries of diabetic patients from among 61,291 obstetric cases.

2. This series illustrates the value of concerted, cooperative efforts by the obstetrician, pediatrician, internist and anesthetist.

3. The best chances for survival were afforded to infants delivered between the thirty-second and thirty-seventh weeks of gestation.

4. Cesarean section is preferred in most cases of pregnancy in diabetes mellitus.

5. The evaluation of the results of pregnancy among diabetic women is measured by fetal salvage.

6. While the infant of a diabetic mother wisely may be considered a premature and treated as such, the associated placenta may be considered as having postmature changes after the thirty-sixth week of gestation.

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Lupus Erythematosus, Discoid and Systemic: One Disease

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LUPUS erythematosus is usually described as occurring in two different forms: the chronic discoid type which affects only the skin, and the disseminated or systemic form with its chronic, subacute and acute varieties. The differences are important enough to make some competent observers believe that these forms are not clinical variants of the same disease but that they are separate disease entities. A comparison of the two forms was felt to be in order to try to determine whether we are dealing with one or two diseases.

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Clinical Features

The contrast is great between the apparently healthy patient suffering only from a patch of erythema and scaling on the cheek and the apprehensive, febrile, prostrate young woman stricken by a fulminating fatal disease. Even the cutaneous lesions are different. The discoid patches show erythema, scaling, follicular plugging, telangiectasia and atrophy; the skin manifestations of the acute form are only erythematous as a rule. However, the discoid patch starts as pure erythema, and old lesions of systemic lupus erythematosus may show all the characteristics of the discoid type.[1] It seems that the character of the lesions is determined by their duration rather than by the clinical form. The site of the lesions is fairly similar, the exposed parts being affected in both types, although lesions of the extremities, covered parts and mucous membranes are seen almost exclusively in the systemic form.

The distribution of the patients according to age, sex and race is similar in both types (table 1). Lupus erythematosus is basically a disease of young women. This is particularly true of the systemic type. In cases of this type of the disease, women outnumber men in the ratio of 5:1, whereas in cases of the discoid type the ratio is about 2:1.

By definition, the discoid type is not accompanied by any clinical evidence of systemic involvement; however, certain abnormalities are detectable by laboratory means,

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TABLE 1

COMPARISON OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS AND ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS

	CHRONIC DISCOID LUPUS ERYTHEMATOSUS	ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS	COMMENTS
Incidence	Young women, 2:1	Young women, 5:1	
Skin lesions	Erythema, edema, scaling, plugging, atrophy, telangiectasia	Erythema, edema	Older lesions of ASLE may resemble those of CDLE
Site	Face	Face, extremities and mucous membranes	
Systemic involvement	Absent	Present	All gradations malaise, fever, arthralgia occasionally in CDLE
Histologic findings	Epidermal changes, marked inflammation, liquefaction degeneration of basal cell layer	Edema, liquefaction degeneration of basal cell layer, fibrinoid degeneration of collagenous fibers	Fibrinoid degeneration of collagenous fibers in CDLE demonstrable with special stains
Laboratory findings	Anemia, leukopenia, thrombocytopenia, increased sedimentation rate, an increase in serum globulin, false positive serologic reaction for syphilis, albuminuria and hematuria may be observed occasionally. Decrease in peripheral blood flow, abnormal serum protein patterns	Anemia, leukopenia, thrombocytopenia, increased sedimentation rate, increase in serum globulin, false positive serologic reaction for syphilis, albuminuria, hematuria and L. E. cells Same changes as in CDLE but more marked and more constant	L. E. cells not found in CDLE
Course	Usually benign	Usually fatal	All gradations CDLE may eventuate in ASLE
Treatment	1. Antimalarials 2. Hydrocortisone is of value when injected into the lesion	1. Corticosteroids 2. Antimalarials may be of value	

as will be described later. The patients appear only superficially well; they tire easily and seem to be prone to repeated minor infections.

Montgomery and McCreight[2] made a study of 286 cases of lupus erythematosus in which the patients were observed at the Mayo Clinic. In 103 of the cases, the disease was classified as chronic disseminated lupus erythematosus. In these cases, multiple patches of the discoid type were disseminated over the surface of the body, a variant of the disease which was formerly thought to be nonsystemic in nature. In many cases, some systemic involvement was indicated by the presence of malaise, fever and arthralgia, and abnormal laboratory findings.

Histopathology

The histopathologic appearance of the two types differs somewhat as might be expected in view of the varied clinical characteristics. Discoid lesions show epidermal changes such as hyperkeratosis without parakeratosis, plugging of the pilosebaceous orifices, isolated keratotic plugging, and a marked inflammatory reaction. In the acute systemic form, the skin chiefly shows telangiectasia and edema. However, observations of the lesions at different stages of their evolution show that the character of these changes is determined by the duration of the lesions rather than by the clinical type. Most old lesions show the abnormalities described under the discoid type.

In addition, both types show liquefaction degeneration of the basal cell layer and fibrinoid degeneration of the collagen in the dermis, around the blood vessels and at the dermal-epidermal junction. McCreight and Montgomery[3] examined specimens by using conventional staining technics, and they were not impressed by fibrinoid changes in the discoid form. However, Stoughton and Wells[4] stained sections obtained in 26 cases of lupus erythematosus, of which 18 were of the discoid type, by the Hotchkiss-McManus method for polysaccharides. They found that the above abnormalities were consistently present in both types of the disease.

Laboratory Changes and Experimental Findings

In cases of systemic lupus erythematosus, the classic laboratory findings include anemia, leukopenia, thrombocytopenia, elevation of the sedimentation rate of the erythrocytes, a decrease in the concentration of serum albumin, an increase in the concentration of serum globulin, a false positive serologic reaction for syphilis, albuminuria, and hematuria. Any of these findings may be obtained in cases of discoid lupus erythematosus but not often.

The L. E. cell is a most consistent finding in the acute systemic form, but, to my knowledge, it never has been found in the discoid form. However, L. E. cells also are missing in many cases of subacute lupus erythematosus, which no one would suspect of being nonsystemic in nature. Similarly, they are not seen in acute lupus erythematosus during remissions. One might speculate that some process at the tissue level may prevent dissemination in cases of the discoid type since the serum of patients with this type of the disease does not inhibit the L. E. phenomenon produced by the serum of patients with acute lupus erythematosus.

Some interesting experimental findings common to both forms of the disease have been reported. Huff, Taylor and Keys[5] studied the peripheral blood flow by means of photoelectric plethysmograms in 14 cases of lupus erythematosus. In 11 of the 14 cases, the disease was of the discoid type. Some degree of slowing of the peripheral circulation was observed in all of the 14 cases, but the slowing was less pronounced in cases of the discoid type than it was in cases of the acute type.

Walker and Benditt[6] used electrophoretic determinations to study alterations in the serum proteins in 13 cases of lupus erythematosus. In four of these cases, the disease was of the discoid type. Abnormalities in the concentration of serum proteins were found in all of the 13 cases, but they were less pronounced in cases of the discoid type than they were in cases of the disseminated type.

Kalz, Telner, Quastel and Van Straten[7] studied plasma changes in 20 cases by means of paper chromatography. In 13 of the 20 cases, the disease was of the discoid type. Although abnormal patterns were more consistent and more marked in cases of the systemic type than they were in cases of the discoid type, they were present in many cases of the latter type.

O'Leary, Lambert and Sayre[8] made an electromyographic study in cases of several different diseases of the skin, including four cases of chronic disseminated lupus erythematosus in which there was no clinical or laboratory evidence of systemic involvement. Abnormal electromyographic tracings were obtained in two of these four cases.

Clinical Course

It is well recognized that, as a rule, discoid lupus erythematosus does not threaten life. On the other hand, and in spite of the advent of steroid therapy, acute systemic lupus erythematosus usually ends fatally. Between these two extremes exist many hard to classify gradations, such as the chronic disseminated discoid lupus erythematosus already mentioned, chronic systemic lupus erythematosus and subacute systemic lupus erythematosus. The existence of these gradations in itself seems a good argument in favor of the unitary theory.

Does discoid lupus erythematosus ever eventuate in the acute systemic form? It does so occasionally, and the transition usually is precipitated by sunshine, trauma or by the use of a toxic drug. This rarity is one of the arguments used by partisans of the dualist theory.

TABLE 2

SYSTEMIC LUPUS ERYTHEMATOSUS WITH DISCOID ONSET

SERIES	CASES OF SYSTEMIC LUPUS ERYTHEMATOSUS	CASES WITH DISCOID ONSET	
		Number	*Approximate per cent*
Montgomery and McCreight[2]			
Before 1938, acute	30	10	33
Before 1938, subacute	44	14	34
After 1938, acute	32	2	6
After 1938, subacute	77	13	17
Wilson and Jordon[1]			
Acute	169	33	20
Subacute	96	25	26
Lamb, Young and Keaty[12]	120	2	2
Shearn and Pirofsky[9]	34	6	18
Dubois[10]	62	2	3
Cohen and Cadman[11]	9	1	11
Allende, Leeper, Rhodes and Lenahan[13]	68	8	12
TOTAL	558*	77*	13.8

*The figures above add to more than the stated total since Montgomery and McCreight's cases were included in Wilson and Jordon's series but were deducted in the final tabulation.

How often does this transition occur? The series of Montgomery and McCreight[2] is divided into cases observed before and after 1938. In 34 per cent of the cases of subacute lupus erythematosus observed before 1938, and in 33 per cent of the cases of acute lupus erythematosus observed in the same period, the disease started as the discoid type. In the cases which were observed after 1938, these respective percentages were 17 and 6 (table 2). The differences between the two groups were attributed to the greater awareness of the disease among internists and to the increased recognition of instances of the disease without cutaneous manifestations.

In 6 of 34 cases of disseminated lupus erythematosus reviewed by Shearn and Pirofsky,[9] the disease started as the discoid type. In one of these cases, 25 years elapsed before a diagnosis of systemic involvement was made. Wilson and Jordon[1] reviewed 221 cases of disseminated lupus erythematosus which had been reported in the literature and 44 similar cases which were observed by Jordon and one of his colleagues. The entire group of 265 cases included the cases which previously had been reviewed by Montgomery and McCreight.[2] In 20 per cent of the cases in which the disease was acute and in 26 per cent of the cases in which it was subacute, the disease initially had been of the discoid type. In 2 of Dubois' 62 cases,[10] in 1 of Cohen and Cadman's 9 cases,[11] and in 2 of the 120 cases reviewed by Lamb, Young and Keaty,[12] the disease also had started as discoid lupus erythematosus.

In 8 of 68 cases of systemic lupus erythematosus recorded at the University of California Hospital from 1937 to 1953, the disease initially was of discoid type. In 6 of 110 cases of discoid lupus erythematosus observed at the same institution, the disease progressed to systemic dissemination.[13]

An interesting relationship between the two forms of the disease has been presented by McCuistion and Schock.[14] They observed a case in which a newborn infant had an eruption which was clinically and histologically

consistent with a diagnosis of discoid lupus erythematosus, and they reported that acute disseminated lupus erythematosus developed in the mother 11 months later.

Treatment

Until very recently, no satisfactory treatment was available for either form of the disease. Great advances in the management of lupus erythematosus followed the discovery that the steroid hormones almost consistently produced remissions in the systemic form of the disease,[15] whereas the antimalarial drugs, ATABRINE®[16] and chloroquine, were found to be of definite value in the treatment of the discoid form.[17-19] However, a few patients with the discoid form of the disease have responded to the administration of cortisone, and, until recently, the antimalarial drugs were not used in treating the systemic form because of the danger of toxicity.

The poor response of discoid lupus erythematosus to cortisone might be attributed to inability of the orally administered drug to reach the lesions, since Goldman[20] and Goldman, O'Hara and Baskett[21] obtained good results by injecting hydrocortisone directly into the lesions. Dubois[22] recently has shown that the antimalarial drugs also are beneficial in the treatment of the systemic form of the disease, and, furthermore, that these drugs inhibit the L. E. phenomenon in vitro whereas cortisone does not.

Comment

No definite agreement has been reached as to whether discoid lupus erythematosus and systemic lupus erythematosus are two different diseases or different forms of the same disease. In a review of the literature starting with the article by Kaposi,[23] which was published in 1872, I found many authors who believe in the unitary concept of the disease. These include Belote,[24] and the following authors of recent textbooks on dermatology: Ormsby and Montgomery,[25] Sutton and Sutton,[26] Becker and Obermayer,[27] and Lewis.[28] Additional support for this opinion is found in recent articles by Shearn and Pirofsky,[9] Jessar, Lamont-Havers and Ragan,[29] Dubois,[30] Michelson,[31] and Page.[32] An excellent and more extensive coverage of the subject can be found in an article by Wilson and Jordon[1] in the American literature and in one by Cohen and Cadman[11] in the British literature.

On the other hand, some authors have expressed doubt that a close relationship exists between these syndromes. Among these authors, one finds Jadassohn,[33] Freshwater,[34] and, more recently, Pastor Fariñas,[35] and Andrews in his textbook, "Diseases of the Skin."[36]

An even stronger voice in favor of the dualist theory is that of George Baehr,[37] who is an authority on the subject. In writing the chapter on lupus erythematosus for the eighth edition of Cecil and Loeb's "Textbook of Medicine," he said that the systemic form of the disease "bears no relationship whatever to that benign indolent lesion known to dermatologists as discoid lupus."

Although chronic discoid lupus erythematosus may be "benign and indolent" at times, it is a potentially dangerous disease. Its classic features may be quite distinct from those of acute systemic lupus erythematosus, but all gradations exist between the two forms. The same gradations are observed in histopathologic studies. With the exception of the L. E. cell, all laboratory abnormalities are present in both forms, although to a different degree. Transition of typical chronic discoid lupus erythematosus into fulminating acute systemic lupus erythematosus does occur. The differences in the response to various therapeutic agents are not as marked as previously thought.

The evidence seems to be overwhelmingly in favor of a unitary theory. To accept this theory is important, for it will avoid dismissing chronic discoid lupus erythematosus as inconsequential. By avoiding exposure to sunshine, by eliminating the use of toxic drugs, by controlling minor infections without unnecessary traumatic procedures, such as the removal of foci of infection, one may help prevent dissemination of the disease. Careful periodic physical examinations and laboratory procedures may detect early changes pointing toward the possibility of

dissemination and may avert this catastrophe.

Summary and Conclusions

Differences of opinion exist regarding the relationship between chronic discoid lupus erythematosus and systemic lupus erythematosus. This question is more than academic because to classify chronic discoid lupus erythematosus as an innocuous disease is to disregard the possibility of its dissemination and to ignore the value of preventive measures which may avert this catastrophe.

I have presented clinical, histopathologic, experimental and therapeutic evidence to support the concept that chronic discoid lupus erythematosus and systemic lupus erythematosus are merely variants of a single disease. Chronic discoid lupus erythematosus should be considered as the mildest form of systemic lupus erythematosus, which may be fatal.

Patients who have chronic discoid lupus erythematosus should be warned about the dangers of actinic radiation, of the use of potentially toxic drugs, of minor infections, and of the indiscriminate removal of so-called foci of infection. They should be checked at regular intervals with physical examinations supplemented by determination of the sedimentation rate of the erythrocytes, by complete blood counts and by urinalysis. These measures should be routine procedures and should be supplemented by a search for the L. E. phenomenon if imminent dissemination is suspected.

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Scientific Exhibit

Streptokinase Intramuscularly in the Treatment of Infection and Edema

JOSEPH M. MILLER, JOHN A. SURMONTE,
MILTON GINSBERG AND FRANK B. ABLONDI*

Modification of Mustard Oil-induced Inflammation in the Rabbit Eye

WHEN mustard oil is applied to the rabbit eye, an inflammatory reaction occurs rapidly, reaching a maximum in two hours. Edema lasts four to eight hours in untreated animals but can be modified by the intramuscular administration of streptokinase-streptodornase.

At present, the only known physiologic activity of streptokinase is its activation of a fibrinolytic system in the animal. It is therefore presumed that the alteration of the inflammatory reaction occurs by intervention of this activated system at the inflammatory site.

Streptodornase has no effect when administered to rabbits.

*Surgical Service, Veterans Administration Hospital, Fort Howard, Maryland (Drs. Miller, Surmonte and Ginsberg); Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland (Drs. Miller and Ginsberg), and the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York (Mr. Ablondi).

PRETREATMENT WITH STREPTOKINASE FOR PREVENTION OF EDEMA

FIGURE 1. Normal rabbit eye.

FIGURE 2. Two hours after administration of mustard oil under the eyelid (untreated control).

FIGURE 3. Two hours after administration of mustard oil under the eyelid of a rabbit pretreated with 100,000 units of streptokinase intravenously.

POST-TREATMENT WITH STREPTOKINASE FOR REDUCTION OF EDEMA

FIGURE 4. Two hours after application of mustard oil; 100,000 units of streptokinase was given intravenously at this time.

FIGURE 5. Approximately five hours after administration of streptokinase.

FIGURE 6. Seven hours after application of mustard oil (untreated control; streptokinase not administered).

FIGURES 7 and 8. Before treatment.

FIGURES 9 and 10. After 48 hours' treatment.

ACUTE CELLULITIS, LYMPHANGITIS AND LYMPHADENITIS

Five thousand units of streptokinase twice a day for three days.

MULTIPLE LACERATIONS AND ABRASIONS

Five thousand units of streptokinase twice a day for three days.

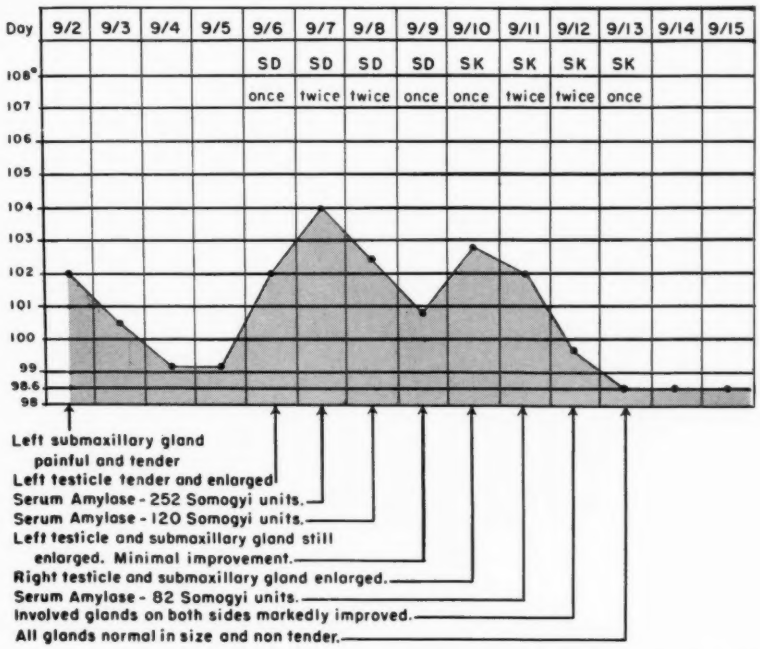
FIGURE 11. Before treatment.

FIGURE 12. After 24 hours' treatment.

FIGURE 13. After 72 hours' treatment.

FIGURE 14. Ten days after trauma occurred.

CLINICAL COURSE OF MUMPS WITH COMPLICATING ORCHITIS



(From Miller, J. M., Surmonte, J. A., Ginsberg, M. and Ablondi, F. B.: The treatment of mumps and complicating epididymo-orchitis by tetracycline hydrochloride and streptokinase. Mil. Med. 118:31-33 [January] 1956. Reproduced courtesy of *Military Medicine*.)

FIGURE 16. Before treatment.

FIGURE 17. After 24 hours' treatment.

ACUTE PURULENT FRONTAL SINUSITIS

Five thousand units of streptokinase twice a day for three days.

(Figures 16 and 19 from Miller, J. M., Surmonte, J. A., Ginsberg, M. and Ablondi, F. B.: Treatment of acute sinusitis with penicillin and the intramuscular use of streptokinase. Laryngoscope 66:143-147 [February] 1956. Reproduced courtesy of *Laryngoscope*.)

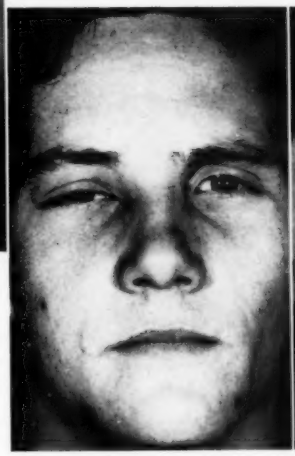


FIGURE 18. After 48 hours' treatment.

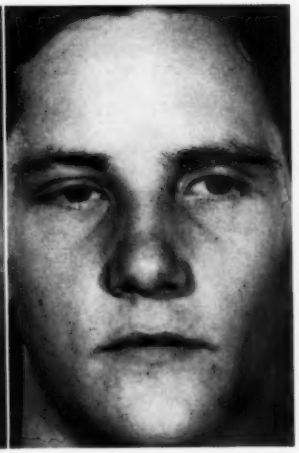


FIGURE 19. After 72 hours' treatment.

CRANIOTOMY BY RIGHT FRONTOTEMPORAL APPROACH

Treatment for three days preoperatively and four days postoperatively with 5000 units of streptokinase twice a day.

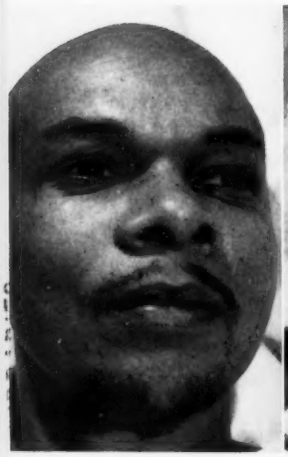


FIGURE 20. Day of operation.

FIGURE 21. Forty-eight hours after surgery.

FIGURE 22. Seventy-two hours after surgery.

FIGURE 23. Ninety-six hours after surgery.

EDEMA AT SITE OF DONOR BONE GRAFT

Five thousand units of streptokinase twice a day for three days.

FIGURE 24. Seven days after surgery, prior to streptokinase therapy.

FIGURE 25. After 24 hours' treatment.

FIGURE 26. After 72 hours' treatment.

CELLULITIS FOLLOWING IMMERSION IN WATER

Five thousand units of streptokinase twice a day for three days.

FIGURE 27. On admission.

FIGURE 28. After 24 hours' treatment.

FIGURE 29. After 48 hours' treatment.

CELLULITIS OF EYE SOCKET

Five thousand units of streptokinase twice a day for three days.

FIGURE 30. Before treatment.

FIGURE 31. After 24 hours' treatment.

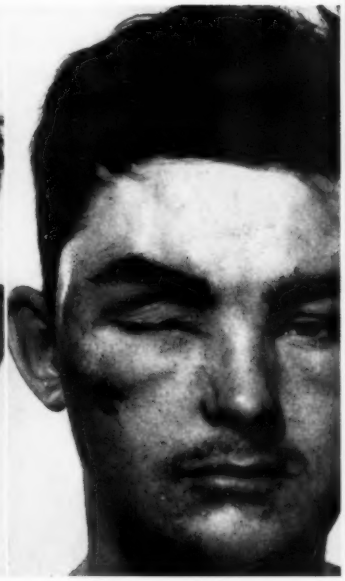


FIGURE 32. After 48 hours' treatment.

EDEMA FOLLOWING EXTRACTION OF TEETH FOR ADVANCED CARIES AND PERIAPICAL INFECTION

Extraction Without Prophylactic Treatment

Treatment with 5000 units of streptokinase intramuscularly twice a day for three days.

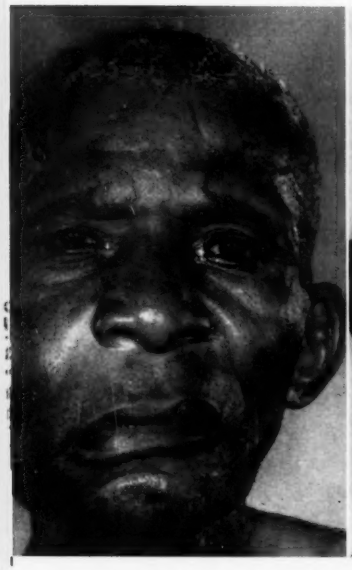


FIGURE 33. Two days after extraction; treatment not yet initiated.

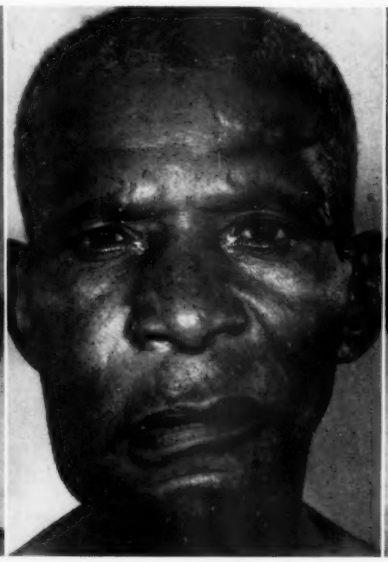


FIGURE 34. Twenty-four hours after initiation of streptokinase.

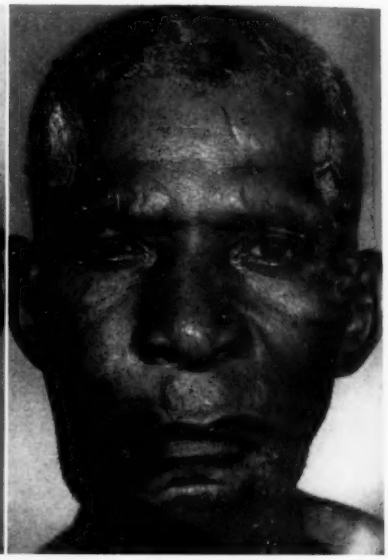


FIGURE 35. Forty-eight hours after initiation of streptokinase.

Extraction With Prophylactic Treatment

Five thousand units of streptokinase twice a day for eight days prophylactically prior to second extraction. Note superior results with streptokinase pretreatment.

FIGURE 36 *(left)*. Immediately after extraction of teeth on left.

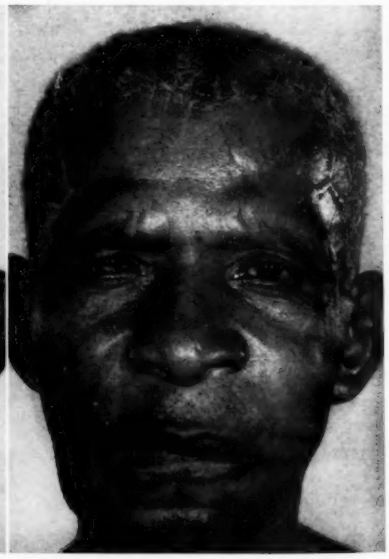


FIGURE 37 *(right)*. Twenty-four hours after extraction.

OBSERVATIONS ON THE INTRAMUSCULAR USE OF STREPTOKINASE

1. Most patients showed beneficial clinical effect after 24 hours.
2. No aggravation of infection.
3. No delay in wound healing.
4. Ten per cent of patients had temperature rise of 2 to 3° F., easily controlled by medication.
5. No changes in peripheral blood picture.
6. No significant alteration of prothrombin time.
7. No fibrinolysis.
8. Some pain and tenderness at injection site in about 60 per cent of cases.
9. No hemorrhage, hematoma or petechiae.
10. No granulomas at injection site.
11. No chills, cyanosis or allergic reaction.

DOSAGE

Five thousand units of streptokinase in 0.5 cc. of physiologic saline administered intramuscularly twice a day for at least six doses. Treatment may be continued longer if necessary. It may be given preoperatively where considerable edema is expected postoperatively.

PRECAUTIONS

1. An antibacterial drug must be given with the intramuscularly administered streptokinase.
2. Streptokinase should not be given to patients known to have defects in the clotting mechanisms.

Intestinal Obstruction

RUDOLF J. NOER*

University of Louisville School of Medicine, Louisville

RUDOLF J. NOER

INTESTINAL obstruction or ileus may be defined as any condition in which there is cessation in the forward progress of intestinal contents. It is never a primary condition but always is secondary to some other disease entity. However, the seriousness of physiologic changes it brings about makes it of primary importance, superseding the disease causing it.

A commonly used classification of ileus or intestinal obstruction divides it into two types, mechanical and adynamic. The mechanical type is produced by something obstructing the bowel from within, pressing on it from without, or growing within the intestinal wall itself. Adynamic ileus, of course, is produced by a relative paralysis of the peristaltic action of the intestine.

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Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

Perhaps a better classification is the one proposed some years ago by Crowley and Johnston, emphasizing the three major causes of ileus. It was based on three conditions: (1) peristalsis, either active or inactive; (2) the lumen, either patent or occluded, and (3) the circulation, either adequate or inadequate. This is a helpful way to remember the pathologic physiology of this condition, and it is important to remember also that there probably is no such thing as a pure case of intestinal obstruction pertaining only to one of these factors. For example, a patient with mechanical obstruction due to an adhesive band pressing on the intestine will, as the condition progresses, also have paralytic ileus because of the protracted distention (i.e., the "silent belly" we find late in the disease), as well as interference with the circulation in the intestinal wall and, under certain circumstances, with the mesenteric circulation as well. Regardless of which condition is the primary one, however, it will help us in managing these cases to remember the importance of these three factors.

The past 50 years have seen a tremendous amount of research as to the cause of death in nonstrangulating intestinal obstruction, with

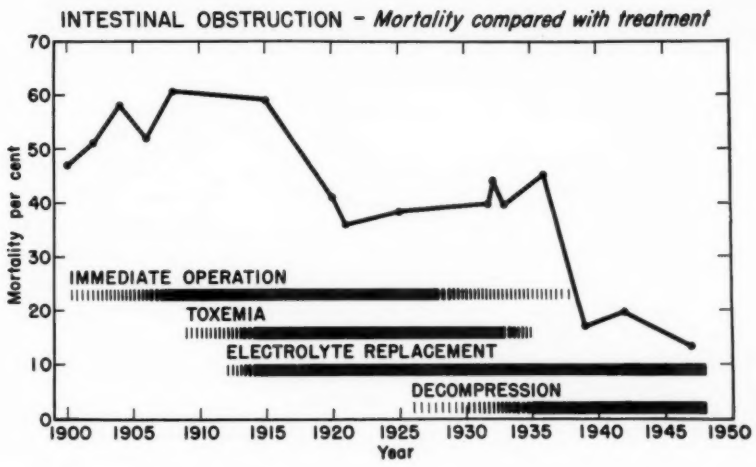


FIGURE 1. Graphic comparison of mortality in intestinal obstruction with ideas as to etiology and treatment.

many changes in viewpoint. In figure 1, I have attempted to correlate the changing concepts of the pathologic physiology with the different ideas as to treatment and the mortality since 1900. In the early part of the century, the mortality rate (and these are unselected figures arbitrarily chosen from the best clinics) varied between 40 and 60 per cent. During this period the dictum was proposed that "The sun shall not set on the unoperated case of intestinal obstruction," and despite the fact that many suns did not so set, the mortality remained between 40 and 60 per cent. Obviously, this was not the answer to the problem of intestinal obstruction.

During the latter part of this period, people were much impressed with the idea of absorption of toxins, so-called noxious split protein products from the lumen of the intestine, and with the need for getting rid of these so-called poisons. This is the period when the so-called Moynihan tube was proposed, an 18 in. glass tube with a diameter of about an inch on which the intestine was threaded while the contents were sucked out, a terribly shocking procedure which, again, did not provide an answer to the problem.

The first notable contribution came in about 1912 through the work of Haden and Orr, who showed that animals with intestinal obstruction lived much longer if they were given salt solution intravenously. Since then, the need for replacing lost fluids and correcting electrolyte imbalance has been generally recognized. This work brought about the first drop in the mortality rate, which still remained around 40 per cent.

The next real drop did not occur until about 1930—the period from 1925 to 1932—when Ward, Wangensteen and others brought forth the idea that decompression was the all-important consideration in these cases. This was based on the work of Herrin and Meek at the University of Wisconsin, who showed that simple distention of an animal's intestines would reproduce all the signs and symptoms of intestinal obstruction. Taylor, Weld and Harrison did similar work in Canada. It was demonstrated clearly that death or illness was not due to toxemia; the picture of intestinal obstruction could be reproduced with balloons which had tubes running through them so that the so-called toxins could be evacuated, while distention continued to make the animal sick. It became apparent that except in instances of strangulation—with its obvious cause of death from perforation and peritonitis—the distention itself initiated the train of events leading to death in nonstrangulating intestinal obstruction. The intestine is distended by gas and fluid and there is loss of fluids into the gut and by vomiting. Electrolyte changes

develop, the patient is dehydrated, and ultimately cellular dehydration probably is the cause of death. The sequence of events is too long and complex to outline in greater detail.

Our primary aims in managing these patients must be (1) to release strangulation if it is present (and we must never make the error of assuming it is not present unless we are reasonably confident of that fact) and (2) to relieve distention. Concomitantly we must replace the lost fluids and correct the electrolyte imbalance.

With this rather brief introduction to the present-day concept of intestinal obstruction, I shall present a patient who had the so-called mechanical type—or, if you wish, occluded active ileus.

DR. JACK MURPHY (resident in surgery, Milwaukee General Hospital): This 34 year old woman entered the hospital with an eight hour history of cramping abdominal pain, nausea and some vomiting. She had had two abdominal operations previously—in 1946 a right oophorectomy and an appendectomy, and in January 1955 a subtotal hysterectomy for uterine fibroids.

Her abdomen was moderately distended, with a minimal amount of generalized abdominal tenderness. X-rays were compatible with complete small bowel obstruction. A Cantor tube was inserted and intestinal decompression carried out for 36 hours. The patient did not improve clinically. Laparotomy was performed through a right paramedian incision. A volvulus involving the small bowel was found and released. There were also dense adhesions in the region of the terminal ileum. The bowel was freed from the adhesions and the peritoneal cavity was closed.

Postoperatively, intestinal decompression was continued for four days. On the fifth day the patient was given sips of water, and she was discharged on the tenth postoperative day.

DR. NOER: The x-rays in this case show the characteristic horizontal fluid levels with the patient in the lateral decubitus position. This patient has recovered completely and is here today. She has no distention whatever. Her bowel function is normal and she feels well.

This case illustrates a number of extremely interesting points. Adhesive band obstruction certainly is by far the commonest cause of mechanical intestinal obstruction, with the exception of strangulation in hernias. It may occur either early or late in the postoperative period. We usually refer to "early" obstruction as that which occurs in the first two or three months after operation, and "late" as 5, 10 or even more years postoperatively. Very early postoperative adhesive band obstruction, such as from adhesions around a ruptured appendix, is very likely to be absorbed completely and cause no more trouble if the patient can be kept completely decompressed. Late mechanical intestinal obstruction usually will not release itself and usually requires operative release.

The diagnosis in this case was properly made and based on several good findings. The history probably is more important in cases of intestinal obstruction than in many conditions. It was characteristic in this case—pain, cramping and intermittent in nature, with reflex vomiting (table 1). The pain was cramping in nature, but the patient told me that between the cramps, which were not very severe, she had a constant dragging pain deep within her abdomen. We have noted this type of pain many times in cases of strangulating types of obstruction. I questioned this patient at some length on that point because this pain appears very similar to that which we sometimes encounter under low spinal anesthesia during traction on the mesentery. When a patient complains of a deep "boring" or "drawing" pain, localized deep within the abdomen, I always suspect there may be strangulation. In this case there was a type of strangulation (which was not complete), a volvulus around

TABLE 1

IMPORTANT POINTS IN THE HISTORY OF PATIENTS WITH INTESTINAL OBSTRUCTION

Pain, cramping and intermittent, with reflex vomiting should make one suspect ileus.
"Fecal vomiting," constipation or obstipation may occur only late and are *not* early symptoms.

an adhesive band, and I suspect that her pain was of the same type that many patients with internal strangulation have.

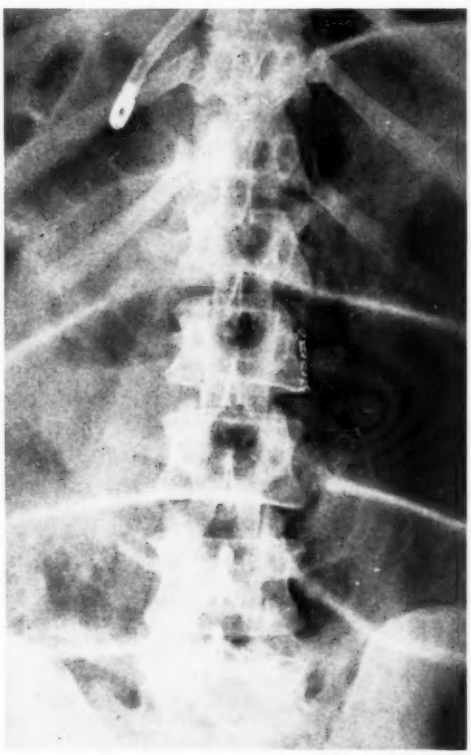
I am told that one of my predecessors at the University of Louisville would bring a textbook of surgery with him into the classroom and read from it the "classic" signs of intestinal obstruction—pain, fecal vomiting, constipation and obstipation—at which point he would dramatically throw the book through an open window and say, "Gentlemen, these are not the signs of intestinal obstruction; they are the signs and symptoms of impending dissolution." I am in complete accord with his viewpoint. Fecal vomiting occurs only in the presence of a gastrojejunocolic fistula, because feces occur only in the colon, not in the small intestine. What most people mean when they speak of fecal vomiting is the vomiting of small intestinal contents. This, too, can occur only when the contents work back from the point of obstruction into the stomach. The first time a patient with intestinal obstruction vomits, the vomited material is not small intestinal contents; it is reflex vomiting of whatever happens to be in his stomach when the cramps hit him. He will continue to empty his stomach and upper duodenum, and the small intestinal contents appear only later as he brings up material from lower and lower toward the point of obstruction. This is a late sign, not an early one, and its absence has no consequence whatever in the diagnosis.

It is also bad teaching to say that "constipation and obstipation" necessarily must be present to establish the diagnosis. Obviously, they occur eventually in any case of complete intestinal obstruction, but if you will remember that obstruction—particularly of the small bowel—leaves a considerable portion of the gastrointestinal tract still present and often still functioning distally, you will see why a patient sometimes has one or two or even three bowel movements after complete intestinal obstruction takes place. Occasionally, we even see a patient with a temporary or transient diarrhea in response to the irritating effect of the obstruction.

The only things that are important diagnostically are the history of pain and cramping,

FIGURE 2. Roentgenogram of patient with intestinal obstruction, taken in erect position.

FIGURE 3. Roentgenogram of patient with intestinal obstruction, taken in supine position.



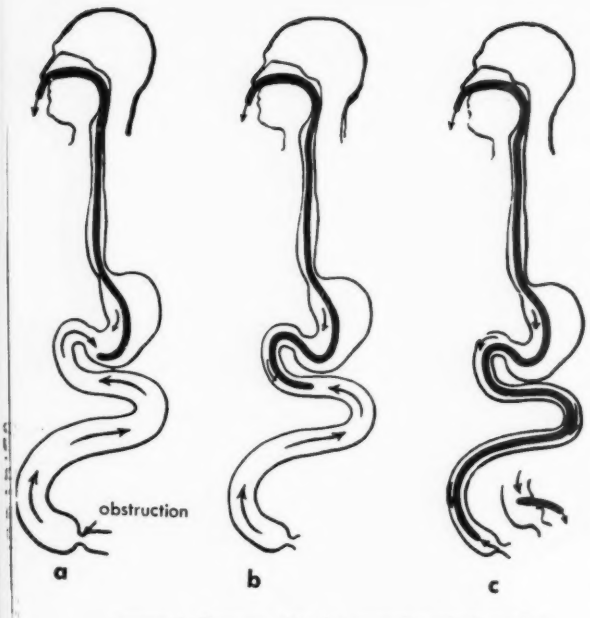


FIGURE 4. Common sites for gastrointestinal suction.
a. Gastric suction.
b. Duodenal suction.
c. Intestinal suction.
Insert. Enterostomy.

reflex vomiting, and the characteristic x-ray findings.

Figure 2 shows a film not unlike the one in the case just described. It was taken with the patient erect and shows the characteristic horizontal fluid level caused by the layering of fluid below and gas above. This is a pathognomonic sign of ileus. The erect film is particularly helpful in making an early diagnosis. If the patient is too ill, one can use a lateral decubitus and achieve the same effect.

Figure 3 is the film of the abdomen with the patient in the supine position. With the patient lying on her back the intestines distribute themselves out more in this manner, producing the so-called stepladder pattern. This film is particularly helpful in distinguishing between small and large intestinal gas. The small intestinal gas is shown in this x-ray, characterized by the fine "herringbone" pattern of the folds within the intestine; the colon is characterized by large, smooth haustral markings, one or two of which are visible in the upper left corner.

In adynamic ileus one commonly sees distention of both the small and the large intestine and not infrequently of the stomach as well. The picture of pure small intestinal distention must be presumed to be due to obstruction of the small intestine until proved otherwise.

So much for the diagnosis. This patient, I am sure, was given electrolytes immediately, was she not, Dr. Murphy?

DR. MURPHY: Yes.

DR. NOER: And a Cantor tube was passed.

Various types of tubes are used for decompression. Figure 4 illustrates the three most common sites at which suction is exerted. On the left is the Levin tube or any other of the stomach tubes. It is by far the most effective means of preventing ileus we have, for it has been demonstrated that the distending gases in ileus are 70 per cent swallowed air. If we can aspirate swallowed air with a stomach tube as fast as the patient swallows it, very few cases of intestinal distention will develop. The stomach tube, however, is not very effective for treating obstruction once distention has occurred, because if the point of obstruction is lower the distending contents must work their way back to the pylorus to be aspirated. I probably should say right here that I no longer believe in reverse peristalsis; in hundreds of fluoroscopic intubations I have yet to find anybody who has followed the patients who has seen a balloon-tipped tube move upward rather than distally. There are some indications that in the duodenum the roentgenologists do see barium reverse itself occasionally, but I believe we should forget about reverse peristalsis in the bowel.

A great advance was made when the principle of duodenal intubation was developed. The passage of a tube through the stomach and into the duodenum made for more rapid and much more efficient aspiration of the distending fluid and gases, since they no longer had to pass the pyloric barrier and get back into the stomach to be aspirated. Since the point at which suction is exerted is much closer to the point of obstruction, a considerable pro-

portion of the patients can be handled by duodenal intubation alone. In a series of some 300 consecutive intubations reported in Detroit a few years ago, adequate decompression was provided in 40 per cent with the tube no farther into the intestine than this.

It remained for the development of the Miller-Abbott tube to provide the most effective means for decompression. Miller and Abbott utilized an old principle first reported in about 1908 by Westermann of Germany, who showed x-rays of intestinal tubes which he had passed throughout infants, in the nose and out the anus. From that time until the early 30s, no one thought anything about passing intestinal tubes, but Abbott and Miller together devised a tube with a balloon tip which they passed through the pylorus, where peristalsis picked up the balloon and propelled it with the tube on downward to the point of obstruction. They were using this method to study the physiology of the intestinal tract. Dr. Johnston of the surgical service in the same institution suggested that, based on the work of Herrin and Meek, use of this tube should be a very helpful adjunct in treating intestinal obstruction. This tube, which passes down through the intestinal tract to the site of obstruction, sucking out the distending gases and fluids as it passes distally, has provided a means for decompressing a large proportion of these patients and has proved very effective in relieving distention during the correction of fluid and electrolyte imbalance.

As with all new methods, many have criticized the Miller-Abbott tube because it is difficult to pass. We once had a resident who was asked about this, and he said, "I never yet knew anybody who thought that the purchase of a cystoscope conferred the ability to use it." I think the same might be said, probably with greater truth, about the Miller-Abbott tube. The purchase of so simple an instrument as the blood pressure apparatus, the sphygmomanometer, does not confer on the purchaser the ability to use it. There are many tricks in passing the Miller-Abbott tube, but the technic can and must be learned to be effective, and it is not the fault of the tube if someone does not know how to pass it.

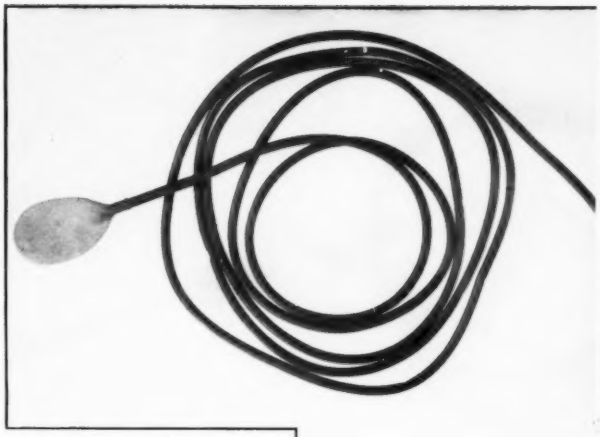


FIGURE 5. Cantor tube.

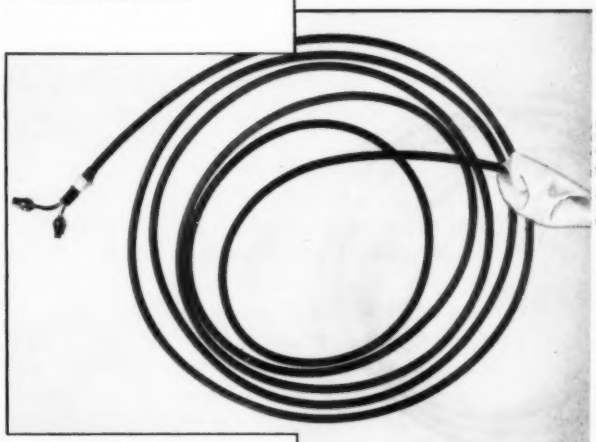


FIGURE 6. Miller-Abbott tube.

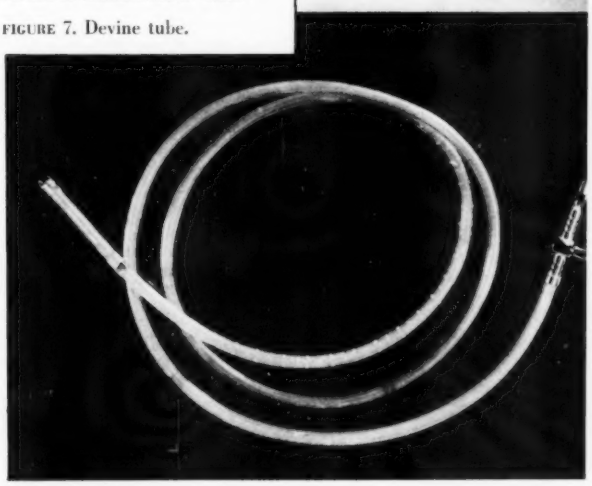


FIGURE 7. Devine tube.

FIGURE 8. Bulb and Y for insertion in suction lines to facilitate flushing tubes to maintain function.

Many modifications of the Miller-Abbott tube have been developed in an effort to make them easier to pass. Among them is the Cantor tube (figure 5) which does not have an inflatable balloon but which has a mercury bag at its end. It depends on the weight of the mercury and gravity to pass gradually from loop to loop down the intestine. It has an adequate lumen for drainage, and is much easier to keep open than the Miller-Abbott tube. In my experience it is a slow and difficult tube to pass; it is the easiest tube to get into the duodenum, but I find it the most difficult to get into the ileum. I dislike very much giving up the advantage of an inflatable balloon which makes it possible for peristalsis to carry the tube to the point of obstruction and also makes it possible for one just to leave the tube lying there by deflating the balloon, at which point there is no further propulsive effort.

Figure 6 shows the Miller-Abbott tube with the inflatable balloon. It has the disadvantage that the larger of the two channels is easily plugged up because of its relatively small size.

A new tube developed by Dr. John Devine (figure 7) has a mechanical gadget for passing it through the pylorus. A few years ago one of my residents said, "If I could get myself a trained angleworm I could get these tubes down." John Devine has done just that—he has devised a trained angleworm. He has put through this tube a four strand cable, with a male fitting at one end and a female fitting at the other, so that they join a half-bent rubber tip, and the little bent end can be turned by rotating a knob. I finally obtained one of these from Dr. Devine and have used it in a number of cases. It is an extremely helpful gadget, the first really good one I have found for getting the tube down quickly.

A helpful means for keeping the tube open and functioning is the brass Y with a bulb (figure 8). One can simply squeeze one tube

FIGURE 9. Diagrammatic illustration of adhesive band obstruction.

FIGURE 10. Photograph of strangulating intestinal obstruction, taken at autopsy.

and flush out the other without having to run and get a syringe.

Figure 9 illustrates diagrammatically the type of thing I am sure was found at operation in the case described earlier, and I compliment the surgeons in charge for not delaying too long when it was seen that the tube was not decompressing the patient. If one cannot pass a Miller-Abbott type of tube within 24 to 36 hours, I think one had better desist and provide relief by some other means.

One should always consider the possibility of strangulation and never resort to intubation if there is any evidence that it is present (figure 10).

The symptoms of strangulation are those of simple obstruction, but more acute and severe and more rapidly progressive (table 2).

In summary, I might refer briefly to the judicious use of intubation, on which I have concentrated because the case presented was a good example of it. First, the tube has only one purpose, decompression, and there is no point in using it if the patient has a clear-cut mechanical intestinal obstruction without distention sufficient to cause physiologic disturbances. The diagnosis of intestinal obstruction does not necessarily mean passing a tube. On the other hand, if the patient is distended but not strangulated, there is good reason to employ decompression before operation. If reasonable doubt exists regarding the presence of strangulation, one should operate at once, not forgetting that in the best of operating rooms it takes an hour or two to set up. That is a golden period during which one can give the patient electrolytes, fluids and, if necessary, blood. Intestinal obstruction demands our best care and constant attention if we are to escape evil consequences and if the patient is to have the excellent recovery represented by the one here today.

TABLE 2

DIAGNOSTIC FEATURES OF STRANGULATING INTESTINAL OBSTRUCTION

Pain and vomiting—Early, severe, persistent.
Distention—Asymmetric early, generalized later.
Tenderness—Often present, localized.
Prostration—Occurs early, progresses rapidly.
All features of simple obstruction, but more acute and severe and more rapidly progressive.

41st Annual

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Cleveland, Ohio, October 22-25, 1956

The Development of Cancer in Mixed Tumors of the Salivary Glands

In former years there was considerable debate among pathologists as to the exact nature of some of the tumors of the parotid and submaxillary salivary glands. Approximately 80 per cent of salivary gland tumors are now known to be mixed tumors and have entirely benign characteristics when viewed microscopically. Several of these cases will be analyzed and a small series of similar cases will be discussed.

EDWARD S. JUDD, M.D.

Staff Surgeon, Mayo Clinic and Associate Professor of Surgery, Mayo Foundation, Rochester, Minnesota

Clinical Discussions of Neurology and Neurologic Surgery

H. R. OBERHILL*

Northwestern University Medical School, Chicago

THE subject of this discussion is such a broad one that we thought it best in the allotted time to present three rather typical neurosurgical patients. Dr. Doxie will describe the first one, a rather typical case of lumbar herniation of an intervertebral disk.

DR. DOXIE: A 32 year old man, a carpenter, was injured in a fall in January (10 months ago). Since then he has had persistent low backache. About two months ago he noted gluteal pain radiating to the left and down the posterior thigh. During the past month this has become so severe that he has been unable to work.

Physical examination discloses tenderness over the distribution of the sciatic nerve at the L_5S_1 interspace and hypesthesia over the L_5S_1 and S_2 dermatomes, with loss of the Achilles tendon reflex on the left.

*Department of Surgery (Neurosurgery), Northwestern University Medical School, Chicago, Illinois.

Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.

(EDITOR'S NOTE: This diagnostic clinic was to have been presented by Dr. Paul C. Bucy of Chicago, but because of a sudden illness it was given by his associate, Dr. Oberhill.)

DR. OBERHILL (to the patient): Will you please stand up, Mr. W., and let us see you walk. He has the rather characteristic posture with a forward stoop and a list to one side favoring the involved leg. Most often these patients will lean away from the involved leg. We do not know why they may lean toward it, although far more commonly they lean away from it.

A rather simple way to demonstrate the Kernig sign and straight leg-raising test is merely to have the patient kick out. Will you kick your right leg straight out in front of you, Mr. W.? What does that do?

PATIENT: It hurts.

DR. OBERHILL: Where?

PATIENT (pointing to left buttock): On the left side.

DR. OBERHILL: Now kick out the left leg. He cannot do that.

I spent part of my neurosurgical training time with Dr. R. Eustace Semmes of Memphis, one of the foremost of neurosurgeons, who is especially interested in the disk problem and who has done some 4000 cases of

lumbar disk herniations. Just recently he presented the results of the last 1500. Dr. Semmes rather cursorily makes the diagnosis in disk herniations, to the point that sometimes the patients are rather taken aback with his examination. He will ask the patient what his difficulties are, and when the patient mentions pain in the back and down the leg and a traumatic history, Dr. Semmes will clear his throat and wink his eye and say, "Kick out your leg, buddy." When the patient kicks out his leg and grabs his back, Dr. Semmes is very certain that the problem is a lumbar disk herniation.

I believe one of the reports from the Mayo Clinic two or three years ago analyzing sciatica stated that in 90 per cent of all cases the pain down the leg is on the basis of either a slipped disk or a tumor, and that in 90 per cent of that group, or in 81 per cent of the total, it is on the basis of a slipped disk; the other 10 per cent may be due to severe osteoarthritis or various other causes. We have found that diabetic mononeuropathy also might fit into that 10 per cent category. In fact, one man who had been referred to us by a very competent internist because of low back pain and sciatica had an extremely "acute disk," so we thought, and we made arrangements for him to be operated on. Thinking we would find a large extruded disk, we found nothing, and much to our embarrassment the urinalysis came back 4 plus sugar. His mononeuritis subsided with diabetic management. That is something we are extremely ashamed of; therefore, we were extremely cautious to see that a urinalysis was done in each of these cases before we operated. Nonetheless such a situation is a rather rare possibility and comprises part of that 10 per cent.

There are certain differentiating points between a lumbar disk herniation and lumbar tumor of the cauda equina at the same level—certain rules of thumb that do not, of course, always apply but are fairly consistent. One is that the disk patient is more comfortable lying down, whereas the tumor patient is more comfortable up and about. Generally when a patient with pain in his back, severe pain down the leg, positive straight leg-raising test, absent ankle jerk or decreased knee jerk, sensory changes, straightening of the lumbar lordosis and scoliosis to one side or the other mentions that he is more comfortable up and about, we always think strongly that it might be a tumor rather than a disk. The theory supposedly is that when a disk patient lies down, the body, in stretching out, creates more space at the intervertebral foramen to allow for the nerve to be relieved of some of the pressure from the underlying disk, whereas in the case of a tumor the nerve is stretched over the tumor and the patient is more uncomfortable when he lies down.

Possibly 60 per cent of persons with lumbar disk herniations never require operation. Absolute bed rest on bed boards for 10 days or two weeks will result in significant improvement if such a patient is going to get well on conservative measures. Occasionally a patient, because of his hesitancy to undergo surgery, may ask that the conservative period be prolonged and in an additional week may show significant improvement that did not appear in the prescribed 10 days or two weeks.

The remainder of these patients are operated on, whether with orthopedic fusion or neurosurgical removal of the herniated intervertebral disk alone—and obviously when there is a neurosurgeon in the room with an orthopedist, when the problem of disk comes up hair flies; the orthopedist believes in fusion of the lumbar spine after a disk removal and the neurosurgeon does not, except in certain instances.

In Dr. Semmes' last 1500 cases of lumbar disk herniation, 50 per cent of the patients had complete relief from back pain and leg pain. Basically this figure does not seem too great, but 40 or 45 per cent had such significant relief that they were able to carry on like normal persons. Five per cent wish they had not seen the doctor. Of these, a sizable percentage are compensation cases who, even though they properly might fit into the category of the 50 per cent with complete relief, are hesitant to admit that improvement until their claims have been settled. The rest of that 5 per cent are patients such as the one I described with diabetic mononeuropathy, or

those with continual low back discomfort and pain down the leg in whom all conservative measures have failed to bring any improvement. Finally in desperation one might say, "The only thing I can do is take a look, assuring you that it is merely an exploration; there might be a disk herniation quite far out laterally which we haven't been able to demonstrate on a myelogram, so let's take a look." Such cases in some instances do comprise a portion of that 5 per cent of patients who wish they had not seen the doctor.

Operative results generally are good, and we believe it is a very successful operation. Some 95 per cent of the patients are able to be up and about, whereas previously they had been considerably disabled. They do not have a new back, so heavy lifting, twisting, shoving, pushing and pulling are not to be done. That is one of the reasons, I think, the orthopedist claims he can return his patient to a heavier type of work by doing a fusion, but as far as we could determine by comparing the findings in a big orthopedic service and neurosurgical service at the same institution the fusion results are no better than those of nonfusion.

Ralph Cloward, a neurosurgeon from Honolulu and formerly of Chicago, has devised an operation which probably constitutes the answer if fusion is to be done. He actually performs a fusion between the vertebral bodies by a rather prolonged operation, with thorough removal of the contents of the intervertebral space, and then puts in bone grafts between the bodies of the vertebrae. Ultimately, from the pictures he has shown us, the two vertebrae plus the intervertebral space filled with bone look like two and a half vertebrae in one piece. This procedure seems to be the answer to the disk problem if fusion is going to be done, but we feel that in most instances it is not necessary.

The next case is one of cervical intervertebral disk herniation, and Dr. Maxwell will give us some details.

DR. MAXWELL: A 52 year old insurance agent in 1950 began to complain of pain about the left shoulder. It was thought to be due to neuritis and responded in a few weeks under conservative treatment. In 1952 the pain recurred, and in addition he had intermittent wryneck. Again the symptoms subsided, and aside from occasional wryneck and mild pain he was well until 1954, when pain recurred with considerable severity. He was hospitalized, and the pain, in addition to involving the back of the neck and left shoulder, began radiating down his arm into the index finger. There was constant pain with numbness of the hand and arm and weakness of the grip, and he was totally disabled.

He was given ACTH and vitamin B and vitamin B_{12}, and heat, massage and cervical traction were employed. Cervical traction provided relief of pain and was continued for 10 days. When it was discontinued and the patient was allowed up, the pains recurred with increasing severity and once again he was totally disabled. He was given another trial of traction and soft collar, without relief.

A myelogram was then made, which substantiated the problem as a disk herniation between C_6 and C_7. The herniated disk was removed surgically and the patient convalesced most satisfactorily. He was able to return to active work and to play golf eight weeks after operation. His difficulty has not recurred.

DR. OBERHILL: The incision in this case was a midline one in which the perivertebral muscles are stripped bilaterally to either side of the spinal processes and laminae two levels above and below the suspected level, and then by removing a portion of the lamina—actually just a very small portion—and pushing the dural contents medially and the nerve root aside the disk material can be picked out.

(To the patient): The pain had involved the left arm, is that correct?

PATIENT: Yes.

DR. OBERHILL: Would you push me away with that arm? Now with the other arm. The strength at present is about equal in both triceps. The triceps reflex had been absent; it is present right now, and just about equal to that on the other side. Do you still have numbness in your fingers?

PATIENT: No, sir.

DR. OBERHILL: Do you have any pain in your arm or neck?

PATIENT: No, sir.

DR. OBERHILL: In our experience only about 10 per cent of patients with cervical disk herniations need to be operated on. Results of conservative management are very good—I would say about 90 per cent excellent results with no further pain in the arm or neck. Of the patients who undergo surgery for removal of a cervical disk herniation, I have yet to see one who was dissatisfied.

In contrast to the lumbar disk operations, in cases of cervical disk we feel it is foolish to try to curet the interspace and we are content to remove only those loose or protruding portions within the spinal canal. In lumbar disk herniations we remove those extruded or protruding portions of the disk and then use curets of progressively increasing size to remove all loose or potentially loose disk material remaining between the vertebral bodies. In the cervical spine there is one great difference: Low in the lumbar area we are dealing with peripheral nerves, the cauda equina; in the neck we are dealing with the spinal cord, and I think practically anybody who has dealt with either the brain or the spinal cord holds the spinal cord in the higher respect because at times, despite careful manipulation, the patient might wake up quadriplegic. It is one of the things we fear above anything, and thus we try to be as gentle as possible and remove only the herniated or extruded portions of the disk and make no attempt whatever to curet the interspace in cases of cervical disk herniation.

We try conservative measures in cases of herniated cervical disk for three to four weeks —cervical traction with 7 to 10 lb. weight— and most patients improve significantly. This man improved temporarily but his condition ultimately regressed and surgery was necessary at that time.

Traction in cervical disk herniation seems to be rational in that a 7 to 10 lb. weight actually seems to open up the interspaces, as shown on x-ray. In regard to Buck's extension for lumbar disk herniations, we feel it is a good way to keep a recalcitrant patient in bed. It is impossible for me to conceive how a 10 lb. weight, or possibly 15 lb., could pull through two such powerful joints as the knee and the hip before exerting any traction in the lumbar interspaces. We do use it on occasion but only for patients who will not stay in bed unless we tie them there.

It has been alleged that a whiplash injury is the commonest cause of cervical disk herniation—the typical whiplash injury being

FIGURE 1. Typical lumbar myelogram, showing a rather large defect in the radiopaque column. The nerve roots are the branches off to the side. The defect proved to be a disk herniation.

sustained when a person sitting in his automobile waiting for a traffic signal to change is bumped from the rear by another car. Only a very small percentage of our patients with cervical disk herniations had any such accident. They have had histories of falls, violent twists and myriads of other traumatic etiologies, but the whiplash injury was down at the bottom of the totem pole.

Figure 1 is a typical lumbar myelogram. You can see a rather large defect in the radiopaque column, the nerve roots being the branches off to the side (the lumbar nerve roots with their sleeves). The defect ultimately proved to be a disk herniation. You all have read statistics that a myelogram is only 80 per cent accurate, with possibly 10 per cent false positive and 10 per cent false negative, but the more of them you see, the smaller the percentage of error becomes. Large defects such as this need not always be present; at times only the nerve root may fail to fill, and a "disk" lying rather far laterally may be one of the most painful. The presence of the nerve root sleeve, that little lip sticking out, on one side and up and down the column and its absence at the place you suspect the lesion can be entirely significant. You might well relieve the patient having only a pea-sized disk herniation lying far out laterally at the intervertebral space and causing extreme pain.

In a typical case of cervical disk herniation the most consistent findings are straightening of the normal cervical lordosis and a narrowing of the interspace itself, with possible osteophytic formation posteriorly—which constitutes a very definite problem if the lesion is of long standing; in addition to removing the disk you may be faced with relieving the pressure on the nerve root at the intervertebral foramen. These osteophytes, no matter how small, may cause a great deal of trouble —like a piece of sand in one's eye.

Figure 2 shows a cervical disk herniation, with the radiopaque column normal on one side and with a visible defect, which at surgery proved to be a lumbar disk herniation.

The third patient had a rather difficult problem with which we are often confronted, that of an aneurysm about the circle of Willis. In this instance it caused neurologic symptoms but did not rupture.

DR. MAXWELL: This 32 year old housewife, who also does office work, has had left-sided headaches much of her life. These became intense in April 1954, and she noted double vision and drooping of the left eyelid, which persisted for six weeks. The headache was felt

FIGURE 2. Cervical disk herniation, with the radiopaque column normal on one side and with a visible defect, which at surgery proved to be disk herniation.

FIGURE 3. Angiogram showing the frontal bone, the distribution of the anterior cerebral artery and of the middle cerebral artery, and the carotid artery coming up from the neck where the injection was made.

in the frontal region, in the eye and above it.

Examination revealed a partial third nerve palsy (the drooped lid), slightly dilated pupil and an outward turning of the eye, and some loss of corneal reflex on that side indicating involvement of the first branch of the trigeminal nerve. Compression of the carotid artery in the neck relieved the headache instantly, and on release of this pressure the headache returned with marked intensity.

A cerebral angiogram demonstrated an aneurysm of the carotid artery which had not ruptured. It was treated by conservative surgery with a slow progressive ligation of the internal carotid in the neck. Postoperatively, the third nerve palsy has disappeared gradually, she no longer has ptosis or double vision or left-sided headaches, and there have been no untoward results of the ligation—that is, no evidence of left-sided hemisphere involvement with right hemiplegia.

DR. OBERHILL: It is apparent from this lady's ocular movements that she has no neurologic deficit. (To the patient): Show us your teeth, please. She has no evidence of facial weakness, or of a hemiparetic gait when she walks. This case is rather unusual, and probably the next illustration will help to demonstrate an aneurysm as it might be seen on an angiogram.

In figure 3 you can see the frontal bone, the distribution of the anterior cerebral artery and of the middle cerebral artery, and the carotid artery coming up from the neck where the injection is made. Possibly you can trace the dye coming up through the neck to enter the base of the skull and then to go on to the carotid before it branches out into the middle and anterior cerebral arteries. This is a rather large aneurysm.

This patient was fortunate in that the neurologic symptoms developed the way they did. The usual story is that with strain or shortly following strain a sudden, severe headache will occur, often described as feeling as though one had been hit in the back of the head with a baseball bat. There may or may not be loss of consciousness and neurologic deficit. The prognosis is unfavorable. Different workers quote various statistics, but I think ultimately

they all agree that this condition constitutes a most serious situation—the rupture of an aneurysm or the mere fact of having an aneurysm. Over-all figures indicate that without treatment 50 per cent of these persons are dead in one year. Roughly about 20 per cent, possibly more, of the fatalities occur with the initial bleeding. Those patients who survive are most likely to have a recurrence of bleeding in the first four to six weeks. Therefore, if the patient is in poor operative condition or if some other reason such as family objection precludes immediate surgery, we keep them at absolute bed rest for four to six weeks. Remember that half of these patients will die within a year unless something is done, making this a rather urgent problem.

As soon as the patient's condition is satisfactory, we obtain an arteriogram to locate accurately the site of the aneurysm. Then, depending on where it stands in regard to the vascular tree, we attack it surgically either by mere ligation in the neck or by direct intracranial approach, or by a combination of these two procedures. We feel, as do others, that aneurysm on the carotid artery itself below the bifurcation or those at the bifurcation or at one of the proximal portions of the middle cerebral artery are best treated by mere ligation of the blood vessels in the neck. Other aneurysms farther out in the tree we attempt always to attack directly by surgery, reflecting an osteoplastic craniotomy flap and isolating the aneurysm under hypotensive conditions. For example, if the blood pressure normally is 130 we might be operating at a pressure of 70 or 75. This shortens the operative time considerably, and if the aneurysm should be torn inadvertently in manipulating it and trying to isolate it, it is a great relief to the surgeon to know that the blood pressure is at hypotensive levels. Patients tolerate the hypotensive procedure very well.

When the lesion has been dealt with, the anesthetist is asked to bring the blood pressure back to normal or possibly even to 10 mm. Hg above the patient's normal level. This permits the correction of any sources of bleeding. All in all, it is a very satisfactory adjunct to surgery.

MEETINGS and Postgraduate Courses

UNIVERSITY OF MINNESOTA, MINNEAPOLIS: Courses to be presented at the Center for Continuation Study, 1956-1957:

General practice:
- Physical medicine, December 6-8
- Urology, January 3-5
- Dermatology, January 7-9
- Emergency surgery, January 31-February 2
- Cardiovascular diseases, February 7-9
- Anesthesiology, February 11-13
- Neurology, February 11-16
- Pediatrics, March 18-20
- Trauma, April 6
- Radiology, April 8-10
- Allergy and chest disease, April 11-13
- Industrial medicine, April 15-17
- Introduction to electrocardiography, May 6-10
- Proctology, May 13-17

Special fields:
- Advances in internal medicine, March 4-6
- Obstetrics, March 21-23
- Advances in surgery, May 23-25
- Ophthalmology, June 17-19

DIAGNOSTIC CLINIC

Cancer of the Mouth and Neck

H. MASON MORFIT*

University of Colorado School of Medicine, Denver

H. MASON MORFIT

A GREAT variety of tumors occur in the region of the head and neck, and I have excluded from this discussion those arising from the thyroid gland or the salivary gland. There are certain general facts concerning the other varieties—those arising from the lip, the floor of the mouth, the tongue, and so on—that help us to understand the principles of diagnosis and treatment, but before I outline those facts there are a few other points I want to make: (1) These are tumors which are accessible; (2) because they are accessible it is possible to diagnose them early; (3) effective methods of treatment are available; (4) we therefore achieve respectable salvage rates in this type of cancer.

These tumors occur in the classic cancer age groups; that is, their peak incidence is in the middle and latter decades of life. They are much more frequent among men than women, the ratio approaching 7 to 1 or 10 to 1.

The pathologic findings are very much alike in every case. Since the mouth is lined with squamous epithelium, in more than 95 per cent of the cases squamous carcinoma is the type of cancer that occurs.

These lesions frequently metastasize to lymph nodes, and this fact has an important bearing on treatment.

Diagnosis

Patients with cancer of the mouth and neck generally have one of three broad presenting complaints. The commonest one, of course, is a sore in the mouth which fails to heal with routine medication. It usually is painless, and the patient may discover it by chance during his daily toilet, or the tip of his tongue may

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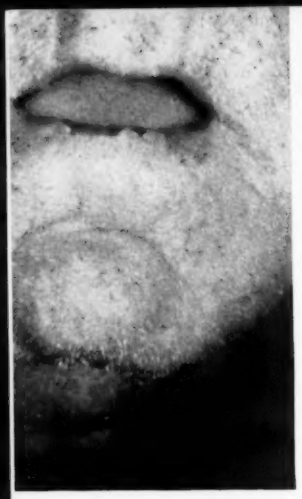
Presented before the fortieth annual Assembly of the Interstate Postgraduate Medical Association at Milwaukee.



a. Carcinoma of the lip.

b. Cancer of the floor of the mouth.

c. Cancer, hard palate.

d. Cancer, buccal mucosa.

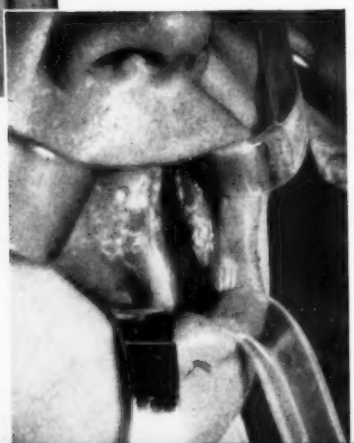


FIGURE 1. General appearance of all mouth cancer is the same, regardless of its site of origin.

encounter a change in contour in one of the various recesses of his mouth, or perhaps he may find that his dental plate no longer fits and he thus becomes aware of an ulcer on his gum.

A second group of symptoms is associated with tumors arising further back in the throat. These patients complain of dysphagia, pain in the ear or referred to the ear and, if the tumor is anywhere in line with the airway, signs of respiratory obstruction.

The third general presenting complaint is a lump in the neck. To the patient, this is the entire complaint. He does not associate it with any lesion inside his mouth. He may find the lump while shaving. Unless the physician is aware that the commonest explanation for a mass in the lateral part of the neck in adults is a metastasis and that there is a primary tumor, probably within the oral cavity, responsible for it, these primary tumors might be missed. The patient has no warning that they exist, and the physician must look for them. To prevent being misled, he must know only this simple fact: A lump in the neck is probably a metastasis and the diagnosis remains incomplete until the primary tumor is found.

The clinical appearance of cancerous lesions of the mouth is very similar in all cases, regardless of their origin. Figure 1a illustrates the characteristic whitish lesion which is called leukoplakia. That term, which simply means "white plaque," seems to be the sum total of the knowledge concerning this disease. We do not know what causes it, and we do not know how to cure it; we simply know that in a given proportion of cases these whitish lesions become full-blown cancers and therefore one must observe them and treat them if ulceration or fissure or some other change occurs.

The same type of white leukoplakic change occurring on a lesion in the floor of the mouth is shown in figure 1b, associated in this case with frank squamous carcinoma.

Figure 1c shows a lesion on the mucosa of the hard palate, and figure 1d a lesion on the buccal mucosa.

These lesions are complicated by the fact that they can be multicentric in origin. In

other words, if we took biopsies from several different places we would find positive lesions at a number of different areas. This occurs out on the skin. Just because a patient has one skin cancer, that does not mean he cannot get another, and unfortunately this complicates the problem of dealing with these mouth lesions as well.

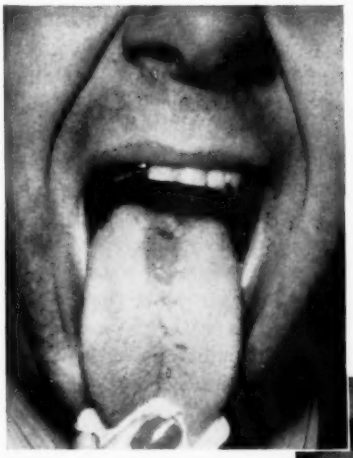
What about a tumor which is not cancer but nevertheless alarms the patient when he discovers it, and therefore he consults a physician? Probably one of the commonest lesions occurring in the mouth, a benign lesion, is a fibroma (figure 2a). Notice the absence of leukoplakic change, the well-defined capsule; it looks like a benign lesion, and it is benign. I do not know of any instance where a fibroma has become a malignant tumor, but you might as well remove it because the patient will keep biting on it, and if you do not take it off he will go to someone who will.

A normal anatomic variant, simple absence of papillae on the tongue (figure 2b), may bring a patient to you because he is worried about its significance, having read the latest cancer article in a lay magazine. This condition characteristically occurs in the location shown in the photograph. Its name is glossitis rhomboidea mediana, but it is not necessary to learn it if you will just bear in mind two facts: that it is benign and that cancer of the tongue practically never occurs in the dorsal mid-line.

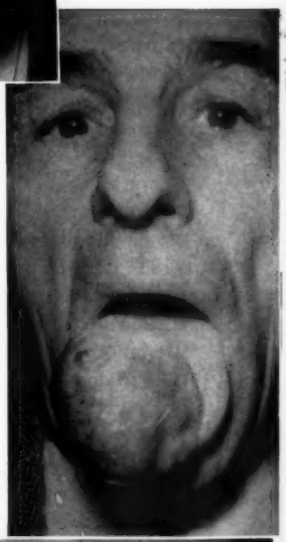
If I mentioned that the lesion shown in figure 2c is a compressible lesion, that it has a purplish hue and that on occasion rather brisk bleeding had occurred from little points of irritation and superficial ulceration, I believe you could recognize it as a hemangioma. These tumors occur on the tongue just as they do in the liver, lung, skin and elsewhere. Again, it is a benign lesion, but of course when it attains the size shown in the photograph it must be removed.

The counterpart to hemangioma, namely, lymphangioma, is a rather rare tumor but one still encounters it occasionally. It is recognizable by the clear, blisterlike blebs which make up the tumor mass (figure 2d). Its microscopic appearance is similar in every way

a. Fibroma of tongue.



b. Glossitis rhomboidea mediana.



c. Hemangioma, tongue.

d. Lymphangioma, tongue.

FIGURE 2. Benign tumors of mouth.

to that of cystic hygroma that one sees in the neck. It infiltrates all the tissue planes of the tongue. It is very difficult to eradicate and can cause a great deal of trouble, although it does not become malignant.

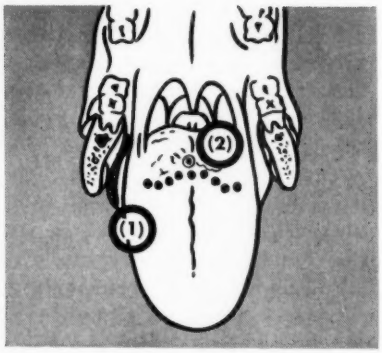
Tongue cancer, probably the commonest form of mouth cancer and a very difficult disease to deal with, occurs primarily in two locations (figure 3a). Two-thirds of the lesions occur on the lateral borders of the tongue; one-third occur on the area which we refer to as the base of the tongue. The latter area is not visible to direct inspection, and the physician can detect the tumors only by palpating the area with a finger or by using a mirror. This is the type of tumor of which the patient will be unaware, and he may present himself with a lump in the neck. It is this type of inaccessible recess that must be searched for the primary tumor.

Tongue cancer occurring in the classic location is shown in figure 3b.

Luetic glossitis is rarely seen today (figure 3c). Syphilis is no longer the threat it once was, but at one time one-third of our patients with cancer of the tongue had positive Wassermann tests, and this undoubtedly was a significant etiologic factor. If you see a patient with a lesion in his mouth, do not exclude the possibility that cancer may be present too, even though his Wassermann test is positive. In fact, I think I can simplify my stand concerning the diagnosis of these mouth lesions by stating that if you see a lesion, do not burden yourself with a lot of clinical criteria which are supposed to enable you to distinguish a tuberculoma or a syphilid or stomatitis aphthosa, and so on, from cancer, because it cannot be done anyway with any significant degree of accuracy. The safest thing to do is to rule out the most serious disease first. Rule out cancer first by means of a biopsy, because it is a medical fact that if you miss the diagnosis of cancer it may result in the death of the patient, whereas a delay in diagnosing a case of tuberculous or syphilitic lesions does not change the prognosis.

Even when patients die of cancer of the mouth and neck, only about 20 per cent have distant metastases. Since, as I indicated ear-

FIGURE 3. Tongue cancer.



a. Topographic distribution. Cancer of the tongue most frequently occurs on the lateral margins (area 1), and is equally common on the right and left sides. The second commonest location is at the base of the tongue (area 2).

b. Tongue cancer in commonest location.

c. Cancer arising in luetic glossitis.

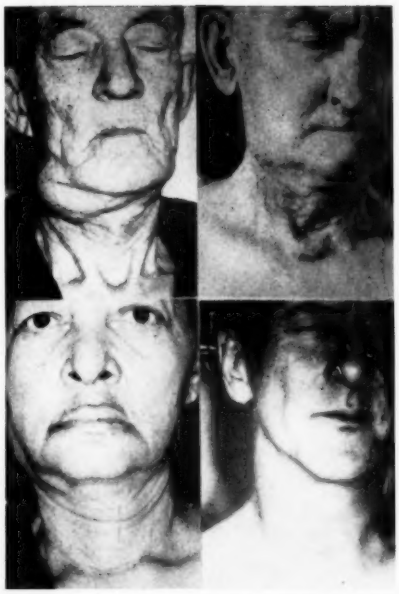


FIGURE 4. The commonest explanation for a lump in the lateral part of the neck in adults is metastatic cancer from a primary tumor located above the clavicle (see text).

lier, these tumors metastasize to the lymph nodes so frequently, one is automatically forced to consider ways of dealing with the metastases in the lymph nodes as well as with the primary tumor. The four patients shown in figure 4 all had the same presenting complaint, namely, a mass in the right side of the neck. In each case the explanation for the mass was different. The man shown in the upper left in the photograph had had radiation treatment for lip cancer two years previously. When the mass appeared in his neck, he did not associate it with the lip cancer, but the mass was metastatic carcinoma.

The patient in the upper right in figure 4, with a swelling on the right side of his neck, had an obvious primary tumor on the right side of his soft palate.

The woman in the lower left part of figure 4 had cancer of the tongue.

The patient in the lower right had a cancer of the floor of the mouth.

As I said, in each case the presenting complaint was the same, a mass in the right side of the neck. All the patients were unaware that the primary tumor existed.

Therapy

Today we have operative procedures which deal rather effectively with these cancers of the mouth and neck, and they carry low morbidity and mortality rates and produce respectable salvage rates. Further, the services of surgeons capable of doing this type of operation are becoming available to more and more areas, so that proper treatment is possible in every case.

The bulwark of therapy, of course, in dealing with the neck nodes is the radical neck dissection, removing all the lymph nodes, including the sternocleidomastoid muscle, the jugular vein around which the lymph nodes grow like beans up a pole, and all the loose adipose tissue in the lateral portion of the neck. The neck lends itself very well, anatomically, to a good, clean dissection. At the conclusion of the operation, only the carotid artery, the vagus nerve, the phrenic nerve and the brachial plexus are left behind. The jugular vein and all the lymph node-bearing tissue has been removed. Since about 1943, with the advent of antibiotics, we have been able to plan and extend our operations to deal with the primary tumor and the regional nodes at one time, and this has led to the so-called combined operations.

The neck dissection is done as a first stage, and then the lower lip is split in the mid-line (figure 5a). The cheek flap is reflected laterally, exposing the inner portions of the mouth, and one can vary the operation to deal with the primary tumors, whether they occur on the tongue, as in the case illustrated in figure 5b, or on the gum. Figure 5c illustrates the resection in a case of cancer of the gum, and figure 5d, cancer of the tonsil. At the conclusion of the operative procedure there is a defect (figure 5e) extending from the hard palate down to the clavicle where the neck nodes were removed. Saliva is draining into the wound, and it is a great tribute, of course, to the antibiotics and anesthesia that despite all this obvious contamination the patient still will recover from the operation—and with a simple

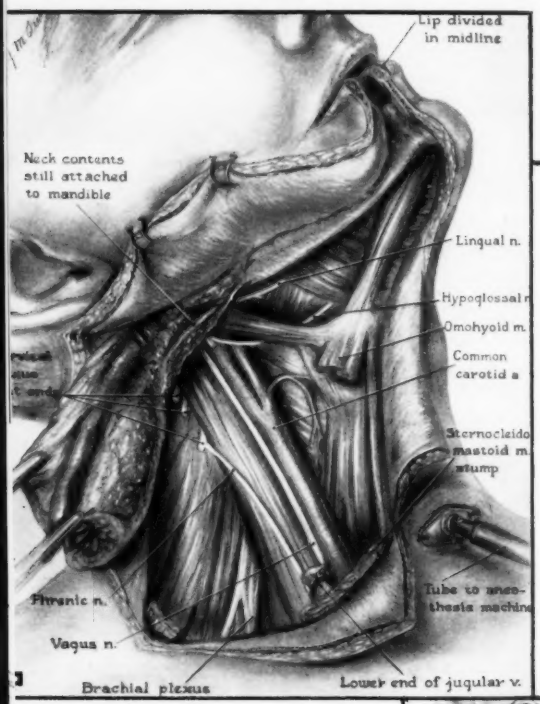
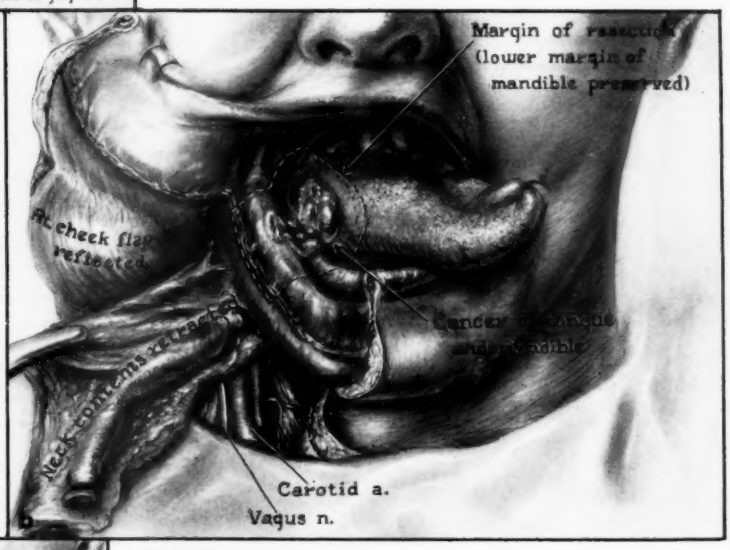
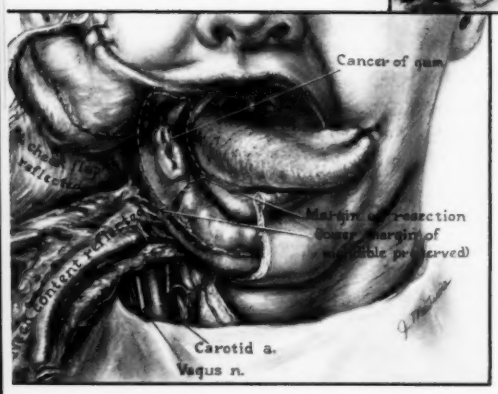
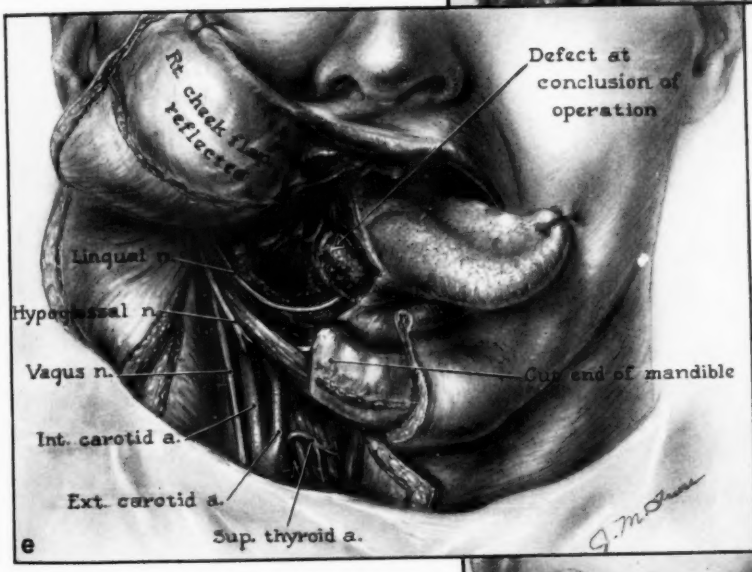


FIGURE 5. Combined neck and intra-oral procedure designed to remove primary tumors and regional nodes at one time (see text).





Cancer
Margin of resection (proximal mandible sacrificed
d


Rt cheek flap reflected
Defect at conclusion of operation
Lingual n.
Hypoglossal n.
Vagus n.
Cut end of mandible
Int. carotid a.
Ext. carotid a.
Sup. thyroid a.
e

Mucosa of cheek sutured to tongue
f

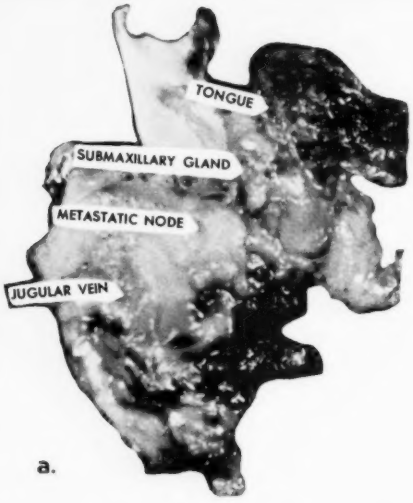
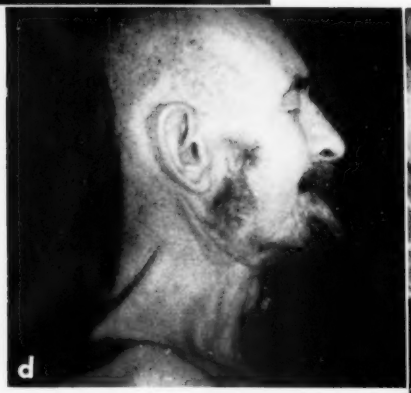


FIGURE 6. Specimens removed in combined procedure and postoperative photographs of patients (see text).

neck dissection the patient may go home in a week. The average hospital stay with the combined procedure is 12 days. Closure is carried out by backing out in the opposite way from the way you went in (figure 5f).

The specimen removed at operation, employing this combined procedure, on a patient with a tumor so large that until this pro-



cedure was available we had no effective way of dealing with it is shown in figure 6a. The cancer on the tongue extended down into the floor of the mouth and on the gum. The operation was an attempt to reach the criteria of the en bloc dissection, so-called, removing the lymph nodes and the primary tumor in continuity. Figure 6b shows the patient after the operation. You can see that if you can preserve the anterior mental arch a very satisfactory cosmetic result is achieved.

The operative specimen in another case in which the cancer started on the gum and grew into the bone, again incurable by any other means than this combined procedure, is shown in figure 6c. Figure 6d is a photograph of the patient taken 10 days after the operation.

If the anterior mental arch cannot be preserved, postoperative appearance will be as shown in figure 6e. Fortunately we do not encounter this complication too often. Most of these intra-oral lesions are located in such a way that they can be removed without sacrificing this mental arch.

The "proof of the pudding" is in the cures. We are curing more than 40 per cent of these patients by means of this type of treatment.

The salvage rates for these various lesions, according to location, are as follows: Our five year cure rate for lip cancer, including all cases both in early and in advanced stages, is about 70 per cent; tongue, 28; floor of the mouth, 25; mucosa of the cheek, 29; palate, 31; gums, 26; tonsils, 18.

In reviewing our results, we divided the material into early and late cases, the dividing line being 2 cm. in size, and found that if we can get patients early—that is, when the lesions are smaller than 2 cm.—we can almost double the curability rate. That finding stands as a powerful argument for the early recognition and effective treatment of these lesions. Our results are not as good as we would like, of course. There still are failures, as is true in all varieties of cancer.

There are two patients here today, and I would like to present them briefly. The first gentleman had a large sore on the corner of his mouth. Apparently he did nothing about it for some months, because when the doctors saw him he not only had a lesion which exceeded 2 cm. in size but he also had metastatic nodules under his mandible. He was treated by the combined procedure I described, with a flap stolen, so to speak, from the upper lip and swung 180 degrees to fill in the defect. A neck dissection was done at the same time.

The second patient had a large tumor in the floor of his mouth, about 3 or 4 cm. in diameter, when first seen. It was invading the root of his tongue and encroaching forward on the mandible, and the nodes under his neck were involved. He refused the recommendation of a surgical procedure and has been treated with radiation therapy.

(To the patients): Thank you for coming.

The patient I just presented will probably go the way of all such patients. That is, they do not die as do persons with breast cancer, for example—with brain metastases, lung metastases, etc. They die from continued lack of control of the disease in the area where it was first encountered, in the mouth or in the neck. Usually, death follows hemorrhage, sepsis, inability to eat due to tumor extension, pain, gradual exhaustion—a long, drawn-out course. It is worth a lot of effort on our part to try to save them from this mode of exodus.

SYMPOSIUM

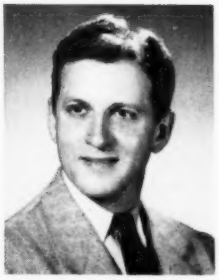
Multiple Sclerosis

PEARCE BAILEY,* ROLAND P. MACKAY† AND FRANCIS J. MILLEN‡

Introduction (Dr. Pearce Bailey, Moderator)

PEARCE BAILEY

ROLAND P. MACKAY



FRANCIS J. MILLEN

THE first complete clinical history of multiple sclerosis was provided in 1835 by Sir Augustus D'Este, a cousin to Queen Victoria and George III, who kept a careful diary describing his strange nervous malady for which he could not obtain a cure. Also in 1835, a London medical student named Robert Carswell was making drawings of the spinal cord of a patient with multiple sclerosis, and a French neuro-anatomist named Jean Cruveilhier was actually beginning a pathologic study of this disorder. Clinicopathologic elucidation of the subject did not come, however, until 1869 when the eminent French neurologist Charcot presented his classic lectures. His attention was attracted to the subject by his observation that his housemaid had intention tremor, nystagmus and scanning speech. Charcot believed at first that she had tabes dorsalis but later revised his diagnosis to "sclérose en plaques," which is known in the United States

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as multiple sclerosis and in England as disseminated sclerosis.

Intention tremor, nystagmus and scanning speech, the Charcot triad, actually is a rare syndrome in multiple sclerosis except late in the disorder, and is also found in other neurologic diseases. However, Charcot, by astute clinical observations and crude methods of free-hand sections and teased specimens with carmine, actually built our present clinical neuropathologic basis of multiple sclerosis. From the standpoints of pathology, etiology and classification, we have not advanced very far beyond his original work.

Charcot demonstrated the essential process of demyelination with a sparing of the axis cylinders and overgrowth of glial tissue, resulting in the so-called sclerotic plaques which can be seen in gross postmortem specimens. Figure 1 illustrates a myelin sheath section of the rostral end of the pons, with numerous clearly demarcated punched-out areas of demyelination, particularly in the pontine tegmentum. The patient was a 42 year old woman who had extensive cerebral involvement—brain stem, cerebellum and optic nerve as well as spinal cord. The largest plaque appears to be in the brachia conjunctiva and thalamo-olivary tract.

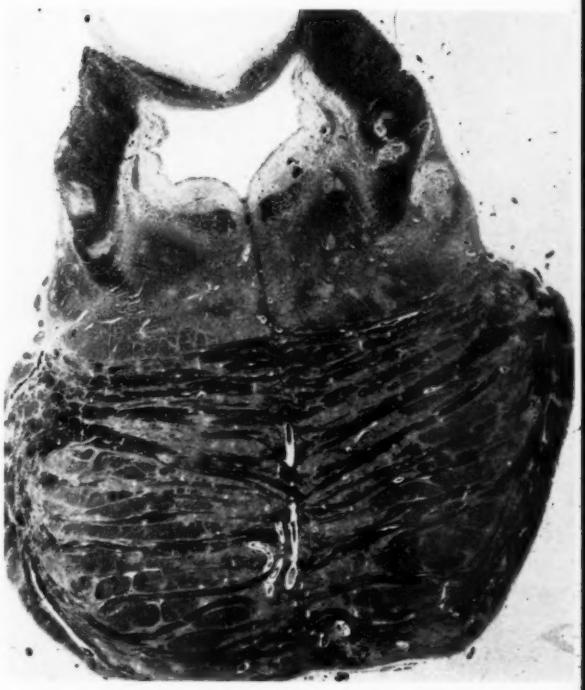

FIGURE 1. Myelin sheath stain of rostral pons, showing numerous perivascular areas of demyelination. (National Institute of Neurological Diseases and Blindness, Case 701.)

New studies on the pathology of multiple sclerosis, particularly those concerned with tissue culture and histochemical technics, promise a growing knowledge.

Dr. Millen will describe the various neurologic manifestations of the disorder, and present some patients. Later, Dr. Mackay will summarize the findings, and we will then take up the problem of treatment.

Presentation of Patients (Dr. Francis J. Millen)

The first patient I shall describe is now 27 years of age. His illness dates back to the spring of 1949 when, at 21 years of age, he experienced an episode of numbness or paresthesia in the leg, difficulty with balance, and inco-ordination of the hands. The symptoms lasted a few days and then disappeared. Three or four months later they returned, and after three months they again abated until the next year. Again in the spring (1950), the patient had the same symptoms, this time with numbness extending up around the abdomen and a girdle type of tightening pain, marked incoordination of the legs leading to staggering, marked clumsiness of the fingers and some difficulty in speaking clearly. He also had odd constricting pains around the knees, and he noticed particularly that vision in his right eye was poor. Some weeks later, vision in the left eye became impaired. He sought medical consultation, and the classic signs of a demyelinating or degenerative disease of the central nervous system were noted—ataxia, spasticity of weak legs, intention tremor, adiadochokinesia, dysmetria, Romberg's sign, generalized hyperreflexia, nystagmus, slurring of speech and bilateral Babinski's signs. Abdominal reflexes already were absent, and the only sensory findings were decreased position and vibratory sensation in the legs.

Laboratory studies were done to exclude other neurologic disorders. Roentgenograms of the skull and spine were negative. Spinal fluid examination disclosed a cellular reaction of 46 lymphocytes, 5 polymorphonuclear leukocytes and 8 red cells. These findings are somewhat unusual in multiple sclerosis and raise the possibility of some other chronic inflammatory disorder such as brucellosis. Other studies were done and other inflammatory diseases ruled out. The spinal protein level was rather high, but the test was done during an acute attack when the patient was almost bedridden. Serologic tests were negative.

During the winter of 1950 the patient's condition improved, and by the next year he had very few residual complaints and returned to work. His reflexes were less hyperactive, plantar reflexes were normal, sensory tests gave normal findings, and in general the neurologic examination was negative. The following year, 1952, he again had fleeting episodes of difficulty with balance. He noticed a marked general fatigue, and blurring of vision recurred. Examination revealed increased neurologic disorder and characteristic bitemporal pallor of the optic disks.

In 1953 he was asymptomatic and had moved to California. He remained symptom-free for almost 18 months and then returned to Milwaukee. After a month or two, an acute exacerbation occurred, with marked staggering, double vision, paresthesia, and pain in various parts of the body. In June there was a remission of all these symptoms. In November he was hospitalized because of a severe exacerbation, and after therapy his symptoms again abated in three months. In March 1955 all the symptoms returned, with more leg weakness, staggering, paresthesia, speech disturbance, vertigo, and disturbance of taste. The latter three symptoms indicate brain stem involvement. In July 1955, remission was almost complete and he felt quite well and returned to work, but in October all the previously noted symptoms recurred.

This young man is here today, and I will ask him to walk out here on stage. He is uncertain about his gait and his stance; as he begins to walk, he is careful. Then he walks with a wide-spaced gait; the spasticity is apparent.

He does fairly well in maintaining balance with his eyes open, but on closing them he immediately loses balance with the slightest tap—Romberg's sign. Trunk ataxia is noted as he sits down. When I ask him to wiggle his fingers, the poor co-ordination is seen. Intention tremor is demonstrated with the finger-to-nose test. It is rather difficult to demonstrate the nystagmus. His face is symmetric, and his pupils are equal.

The patient tells me he is now working at the post office. Actually, although he had a recent exacerbation, he is beginning to improve considerably. There is slight scanning and slurring in his speech, and his arms are rather spastic.

Physical signs may change from day to day in patients with multiple sclerosis, particularly when they are under treatment. Just the other day, examination disclosed a strong Hoffmann sign in this young man; we are now unable to demonstrate this important finding, which is evidence of corticospinal tract involvement. His upper reflexes actually are hypoactive; the knee jerks show some improvement over the hyperreflexia he had previously. He has been under treatment at the Veterans Administration Hospital. The Babinski sign can be seen—the large toe draws up on plantar stimulation, with fanning downward and outward movements of the smaller toes—as can the Rossolimo reflex. The Stransky test is negative.

On sensory testing, very few changes are found in some of the earlier stages of multiple sclerosis, but the most common are those of decreased vibration and position sense. This patient is able to feel vibratory sensation in the arms and at the wrist but not in the feet. In the upper extremities he is able to distinguish pinprick, sharp or dull. There is some loss of pinprick sensation in this disorder that may vary from patient to patient. In this case we find at present a decrease in pinprick sensation, not too characteristically found.

I am unable to show you the optic neuritis or the bitemporal pallor of the disks, but they are present, and the abdominal reflexes are both absent.

The second patient is 52 years of age. He cannot recall whether or not he had any symptoms early in life, but at about age 29 there were some complaints recorded by a local physician of neuralgialike pains in the left shoulder and some difficulty in writing, of several months' duration. This episode was forgotten, and almost 10 years later these peculiar pains recurred in the left arm and shoulder, spread to the face, and were associated with difficulty in balance, inco-ordination of hands and disturbances in speech—all this without any history of infection, injury or other traumatic incident, toxin or the like.

The disease really began in 1943 as far as this patient is concerned, the symptoms being chiefly those of diplopia and staggering gait. Examination then showed rather characteristic findings—the Charcot triad and other signs of ataxia, Romberg's, Hoffmann's and Babinski's signs, and generalized hyperreflexia. After a remission in 1944, he had an exacerbation of the same type of pain, some paresthesia, fleeting pains in the arms, hands, legs and feet, and weakness in the right arm. These symptoms began to clear, and another remission followed. By 1946 another exacerbation occurred, with more poor balance and also with sphincter disturbance, more visual impairment, and brain stem involvement. In 1947 these symptoms persisted, slowly progressive now, and in 1948 the diagnosis of multiple sclerosis was established at a large clinic.

His course has been characterized by remissions and exacerbations. For almost three years (1949 to 1951) he was unable to work, but then he had a remarkable remission and was able to return to work. In 1953 he again had a recurrence of all symptoms and signs, and since then there has been a gradual progression of the findings in all areas. He is able to walk with a cane, and gets along with sheer will power. He was a very successful engineer.

The next patient's illness began only three years ago, at the age of 36 years, and he has very marked dysmetria, adiadochokinesia, intention tremor and gross nystagmus. There is loss of position sense, and speech is clumsy and difficult.

I believe I have mentioned most of the neurologic findings in multiple sclerosis, and the patients here have represented various stages and the progression of the disorder. The two younger men, who in youth had remissions and exacerbations, are still having periods when they are relatively symptom-free.

Summary of Findings (Dr. Roland P. Mackay)

There is no serologic, immunologic or other chemical diagnostic test to identify multiple sclerosis. It is diagnosed only by a physician familiar with its typical clinical behavior, and consequently it is a matter of individual judgment. I would not have you believe the diagnosis is a trite affair or an easy one. Any physician can diagnose multiple sclerosis if the history is typical—if it begins after the age of 10 and before the age of 50 years with an up-and-down course of exacerbation and remission, appearance of new symptoms often quite different from any the patient experienced previously, or sometimes reduplication of previous exacerbations from which the patient apparently had recovered. Further, this picture of dissemination in time—that is, exacerbations and remissions—is often associated with dissemination in space. In one attack, the patient may have blindness in one eye, from which he may recover; at another, both legs may be paralyzed, and he may recover; at a third attack he may have incoordination and clumsiness, intention tremor and so on, indicating cerebellar involvement. With all these typical findings in a patient who has had the disease long enough, anyone can make the diagnosis.

I defy anyone to diagnose multiple sclerosis in a case such as the one I encountered some years ago, that of a 16 year old girl who awakened with a left hemiplegia. I examined the girl, finding a left hemiplegia with increased tendon reflexes on that side and with a Babinski sign and all the rest, and absence of abdominal reflexes on that side. She did not have heart disease or any other condition which could account for hemiplegia, so I could tell the mother only that her daughter had hemiplegia. Spinal fluid was normal. Within six weeks the girl was perfectly normal, but

a year later, while at work at a soda fountain, she suddenly fell down, paralyzed in both legs. She recovered from that episode also, but now some years later she has a typical picture of multiple sclerosis. One does not make the diagnosis after the first attack.

Dr. Millen mentioned the abnormal spinal fluid findings in some of his cases. At least half, and perhaps three-fourths, of patients with multiple sclerosis have normal spinal fluid. We are now studying the gamma globulin content of spinal fluid and we have found that in 75 or 80 per cent there is some elevation of gamma globulin in the spinal fluid.

To diagnose multiple sclerosis, one must demonstrate that there is no other cause, such as syphilis, for the neurologic complaints. Neurosyphilis in some respects may imitate multiple sclerosis. It is always wise to examine the spinal fluid and try either to establish an absence of other disease or to find an elevation of the gold curve in the first or second zone, or perhaps a mild increase in cell count, or some increase in proteins, and now, by modern tests, some elevation in gamma globulin.

It is very difficult to summarize the picture of multiple sclerosis so that you can recognize even the next typical case that you see. There are some things that the disorder does not do. It rarely begins after the age of 50 years. Do not make the diagnosis in a patient whose first symptoms appear at age 60 or 65 years; he does not have multiple sclerosis. Multiple sclerosis is a disease of degeneration whose cause is unknown and which attacks the white matter of the nervous system. It does not attack gray matter, and consequently there are some clinical syndromes involving the gray matter which multiple sclerosis cannot imitate. For example, cogwheel rigidity, a rest tremor or a masked face does not occur in multiple sclerosis because those symptoms arise from disease of the basal ganglia, which are gray. A patient with multiple sclerosis does not have the focal muscular atrophy seen in progressive muscular atrophy or amyotrophic lateral sclerosis, nor does he have the claw hands one sees in the latter disease. Why? Because they represent involvement of the anterior horns of the spinal cord—gray matter. Paroxysmal sleep attacks do not occur in multiple sclerosis; they are due to involvement of gray matter. One could go on and mention other symptoms which do not appear in multiple sclerosis.

I want to emphasize one highly important point. All of us doing clinical neurology see patients who have been told they have multiple sclerosis when they do not. Publicity in the lay press has made the disorder extremely popular. Do not reveal the diagnosis of multiple sclerosis to a patient under any circumstances unless you are sure.

Dr. Bailey will conclude by indicating some measures that are necessary in treatment, and some of the paths along which research is being conducted.

Treatment

DR. BAILEY: Treatment of multiple sclerosis has been one of the tragic stories of medicine. Many false hopes have been raised, largely by two facts: (1) Multiple sclerosis is frequently misdiagnosed; (2) the disorder is an alternating one, as a rule, with exacerbations and remissions. Therefore, it is extremely difficult to test a particular medication, and not until recently has some system been organized to do this effectively.

Treatment methods were approached first from the etiologic standpoint: What is the cause, and can the cause be treated? Another approach has been to devise some method of stopping the progress of the disease without knowing the cause. Still another approach has consisted of empiric tests—"shotgun" procedures—to see if, by chance, a substance could be found that would arrest the progress. A fourth method, rehabilitation, has more or less come into vogue since World War II and aims at maximum neuromuscular retraining and socioeconomic adjustment on a level compatible with the patient's disability.

As to etiology, there has been the infectious theory, as you know. First it was a virus, then a spirochete, and more recently in Europe an acid-fast bacillus has been implicated, in the opinion of some. Another theory has concerned allergy, and it was given considerable force by the production of experimental encephalomyelitis in guinea pigs and monkeys

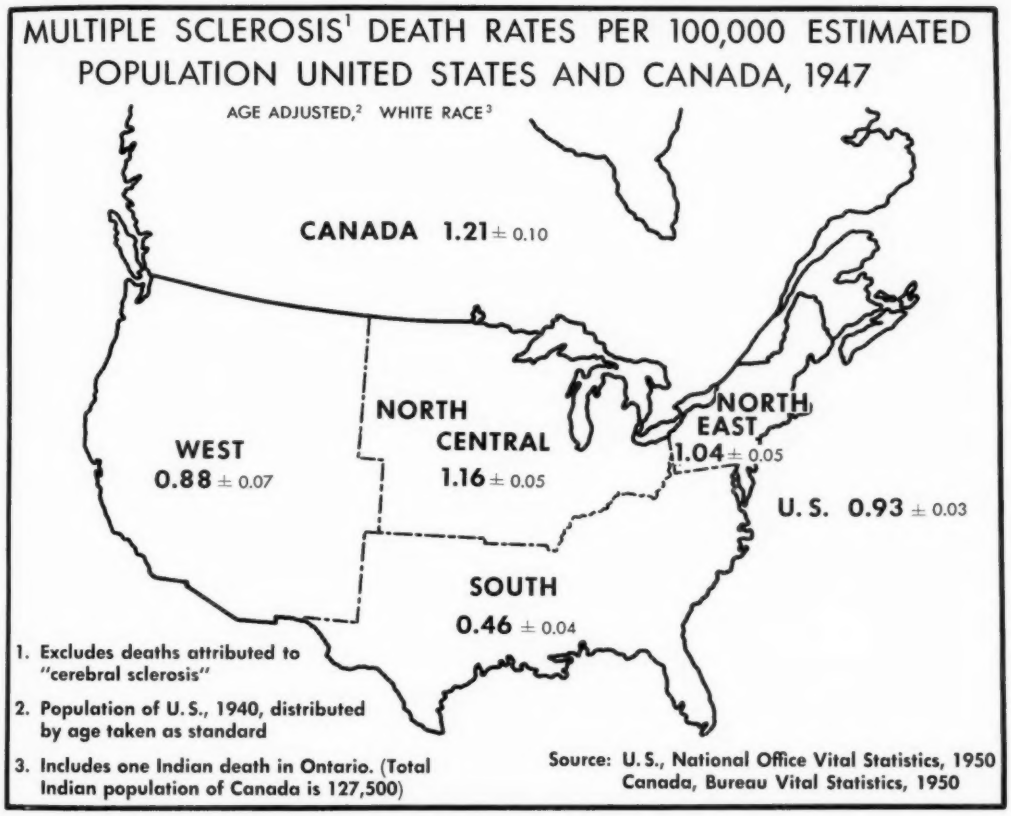
MULTIPLE SCLEROSIS[1] DEATH RATES PER 100,000 ESTIMATED POPULATION UNITED STATES AND CANADA, 1947
AGE ADJUSTED,[2] WHITE RACE[3]
CANADA 1.21 ± 0.10
WEST 0.88 ± 0.07
NORTH CENTRAL 1.16 ± 0.05
NORTH EAST 1.04 ± 0.05
U. S. 0.93 ± 0.03
SOUTH 0.46 ± 0.04
1. Excludes deaths attributed to "cerebral sclerosis"
2. Population of U.S., 1940, distributed by age taken as standard
3. Includes one Indian death in Ontario. (Total Indian population of Canada is 127,500)
Source: U.S., National Office Vital Statistics, 1950
Canada, Bureau Vital Statistics, 1950

FIGURE 2. Comparison of mortality rates for multiple sclerosis according to geographic areas. (From Kurland, Mulder and Westlund: New England J. Med. 252:649-653 [April 21; April 28] 1955.)

both by injecting homologous brain extracts into the brain and by injecting homologous brain extracts with dead tubercle bacilli intravenously and intramuscularly. Proof is lacking that the disease or the demyelination produced by these injections is actually multiple sclerosis.

The question of arresting progress of the disease came out of recent studies on environmental or climatic influences. Kurland at the National Institute of Neurological Diseases and Blindness demonstrated a predominance of multiple sclerosis in the northern sections of most countries as compared with the southern sections. He and his co-workers found that the Northeastern and North Central States and even the Western States have much higher mortality rates for multiple sclerosis than the South (figure 2).

Table 1 compares the prevalence of the disorder based on mean January temperatures. Notice that the incidence is much higher in Winnipeg, for example, than in New Orleans. Would it do any good to send a patient to Florida or Arizona? I do not know of any conclusive evidence to justify such a move, but the question has not been studied adequately. My advice would be that if moving from Milwaukee to Miami, for instance, would not impose social or economic inconveniences on a patient, he may as well do so. (I have no Chamber of Commerce interests.)

Another question has been that of nutritional deficiency, and in areas lacking cer-

TABLE 1

CHARACTERISTICS OF THE FIVE COMMUNITIES SELECTED FOR THE INVESTIGATION OF MULTIPLE SCLEROSIS*

COMMUNITY	LATITUDE (Degrees North)	MEAN JANUARY TEMPERATURE (Degrees Fahrenheit)	PREVALENCE RATIOS ON JANUARY 1, 1949 (Per 100,000 population)	"CORRECTED PREVALENCE RATES" ON CLINICAL REVIEW (Per 100,000 population)
Winnipeg	50	–3.5	42	40
Boston	42	28	41	
Denver	40	31	38	
San Francisco	37	50	30	
New Orleans	30	55	13	6

*From studies of Kurland, Mulder and Westlund (New England J. Med. 252:649-702 [April 21; April 28] 1955).

tain minerals it has also been suggested that a deficiency of mineral metabolism might play a role in multiple sclerosis. Swayback in lambs has been transmitted to humans in regions where the disease occurs. However, further investigations have not provided evidence that multiple sclerosis results from any mineral deficiency.

Studies also have been carried out on the relation of fat diets to multiple sclerosis, and here again there is no very substantial evidence to bear out any conclusions.

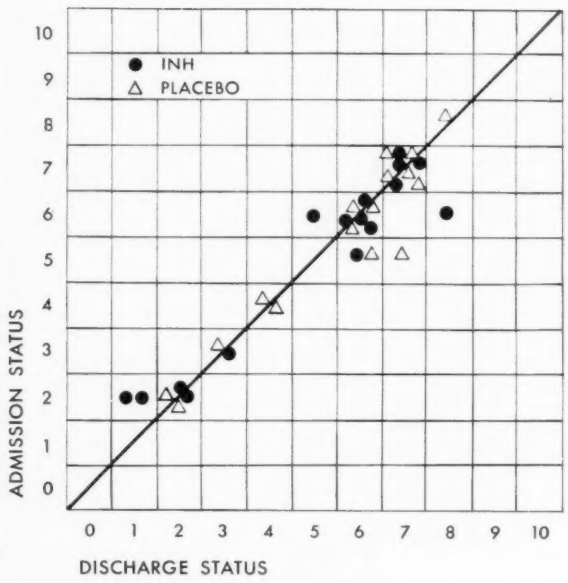

FIGURE 3. Effect of isoniazid in multiple sclerosis. (From Korengold, M. C. and others: Neurology, vol. 5, November 1955.)

Rehabilitation has been of considerable value in selected cases—that is, supportive treatment with a very individualized approach plus a comprehensive rehabilitation program. The patient must have a program; he must be retrained in improving his daily living, in neuromuscular function, and also to make a socioeconomic adjustment. Of course, rehabilitation is not too encouraging in a progressive disease. From what I have seen of such efforts in selected cases, I would say that one must be very careful not to set the therapeutic goal beyond the patient's limits. In many cases considerable increase of happiness and productivity has resulted.

In 1954, Kurtzke and Berlin made a study in New York of the effect of isoniazid in multiple sclerosis, and the results were rather optimistic. There was general improvement in many cases, and in one or two cases the exacerbation or its progress was stopped. When isoniazid was discontinued, the exacerbation returned.

Multiple sclerosis is such a crippling disease and covers such a long period in the average patient's life that almost anything of promise, I think, should be provided. Therefore, we decided to test the results of the New York study at the National Institute of Neurological Diseases and Blindness as a pilot program, but under much more rigid control conditions. We asked for 82 patients and set

up rigid diagnostic criteria: (1) age between 15 and 25 years; (2) history of at least two episodes; (3) all other possible diagnoses ruled out; (4) no complicating factors that would interrupt the study (convulsive seizures, extreme emotional instability or social or economic factors). These patients were referred by physicians in private practice. An incorrect diagnosis had been made in 17 of the 82 cases, almost 20 per cent. We established "incorrect diagnosis" not by exclusion but by making another diagnosis.

The most common incorrect diagnosis was cerebellar ataxia. The second most common was psychoneurosis. Third was a miscellaneous group of conditions including brain tumors, spinal tumors, cervical arachnoiditis, and recurring cerebrovascular disease.

The rigid screening process excluded all but 32 patients from the study. We placed 16 patients on isoniazid, and the other 16 were given a placebo which could not be distinguished from the drug either by the patients or by the neurologists who were conducting the study. Only one person in the entire project knew which patients were receiving isoniazid.

The results are illustrated in figure 3. The vertical ordinates represent admission status; the horizontal abscissas, discharge status. The functional categories were devised by Kurtzke and Berlin. The higher the category, the lower the function. Category 10 would be a dying patient; 9, a totally bedridden patient; 8, a bedridden patient able to use his arms; 7, a wheel chair patient; 6, one using braces and crutches. Actually, the important point is category 5, because above it there is no productivity for work, whereas below it there is. Zero indicates complete functional capacity but the presence of a few neurologic signs.

By following the diagonal line which bisects the boxes, you will notice that usually there was no change in status either with isoniazid or with the placebo. However, the only patients who did show improvement were those who received isoniazid. None of the patients who received the placebo (indicated by the triangles) were improved.

The Veterans Administration is conducting a similar study in 30 hospitals, and their results should be published rather soon.

Great strides are being made in our knowledge of multiple sclerosis, particularly in relation to tissue culture and histochemical studies on the problem of myelinization. You have heard a great deal about loss of myelin, but there also seems to be a problem of synthesizing myelin, and actually the process of demyelination may be proved to be more of a defect in the synthesis of myelin than a result of its destruction. It appears that a certain type of neuroglia, particularly that of oligodendroglia, plays an important role in this function.

I believe that with the research going along, in particular the studies which the electron microscope and with tissue culture, patients with multiple sclerosis in the future will have a more hopeful outlook.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital
Hines, Illinois

Report of Case

DR. ROLAND R. CROSS, JR. (Attending Surgeon, Urology): On February 11, 1948, a 48 year old white man was transferred to Hines Hospital. He had received treatment for general paresis at a neuropsychiatric hospital. In August 1945 he had a course of therapy with typhoid vaccine for the paresis. In 1948 he had malaria, which was controlled without difficulty by quinine.

The patient complained relatively little about his general physical condition, which is not too surprising—he had paresis. After malaria treatment, however, he had difficulty in voiding. Heat and sitz baths did not help him and he was catheterized. After that, he had to be catheterized repeatedly. Rectal examination disclosed a mass about the size of a lemon beginning in the distal portion of the prostate. The apex of the mass could not be reached with the examining finger. The rectal mucosa in the area was smooth and normal.

Cystoscopic examination revealed a markedly elongated posterior urethra and bladder neck, a usual finding in cases of prostatic enlargement. The cystoscope was too short, however, to visualize any portion of the bladder except about 60 degrees of the anterior arc, where a cauliflowerlike mass and general irregularity of the bladder mucosa were seen. Turning the cystoscope would cause it to impinge on the tissue within the bladder, so the rest of the bladder could not be visualized. A cystogram revealed marked irregularity of the bladder outline and large filling defects.

The patient's only spontaneous complaint regarding the urinary tract was the difficulty in voiding. He had never noted any burning on urination or blood in the urine. Previous urinalyses, in August and December 1947, had revealed no blood, either gross or microscopic, and only an occasional white blood cell. An inlying catheter was inserted and urine drained in copious amounts.

The complete absence of hematuria up to December 1947 is remarkable; the nature of the tumor at examination would suggest that it had been present for some time. The physicians who saw the patient felt that he had carcinoma of the bladder, and he was transferred to a general hospital. He appeared chronically ill and had lost weight, but it was stated that this could be explained to some extent by the malaria treatment.

The heart was essentially normal; the lungs were also normal. The abdomen was distended but otherwise normal. Results of rectal and cystoscopic examination were essentially the same as noted previously. Neurologic findings were compatible with the paresis. There was slight speech defect with test phrases. Evalua-

tion of mental processes disclosed that he had made remarkable progress on antisyphilitic therapy, and a memory defect had improved considerably. He did not have hallucinations or illusions. Aside from moderate emotional flattening, there was no gross evidence of psychosis beyond a mild deterioration. Speech was coherent, and the patient was in fair contact. The diagnosis at the time of his discharge following his first period of hospitalization was carcinoma of the bladder, probably papillary, and psychosis due to syphilis of the central nervous system.

On admission to Hines Hospital on February 11, 1948, the history and physical findings were essentially as already described. There was no inguinal lymphadenopathy. On rectal examination, the prostate was broad and irregular as far as the finger could reach.

Notice the difference here between the two reports: At the other hospital, it was stated that the mass was lemon-sized and began at the upper border of the prostate; here, the mass and the prostate are mentioned together as one feature of the rectal examination.

The seminal vesicles were not palpable. The urine contained white blood cells, 4 plus, which would certainly be compatible with repeated catheterization. Intravenous pyelograms were unsatisfactory due to gas in the large bowel. Evidently, however, the left kidney appeared to be large. Dye did not appear in the bladder after 30 minutes, which suggests that the tumor, or whatever it was, was blocking the lower urinary tract, probably in the region of the ureteral orifices. The value for nonprotein nitrogen in the blood is not reported. One would expect, with the failure of the intravenous pyelogram to show up very well, especially with no dye in the bladder after 30 minutes, that probably the nonprotein nitrogen was elevated. This certainly would be in keeping with a mass in the region of the trigone and prostatic urethra.

Cystoscopic examination at Hines Hospital showed large clefts in the sphincter, corresponding to the position of the hands of a clock at 10 o'clock and 1 o'clock, with marked intrusion and nodular irregularity. There was some necrosis of the mucous membranes of the floor with considerable necrotic material on the surface. There was so much intrusion that the bladder was not well visualized, which corresponds with the previous cystoscopic examination. The pathologic process had appeared to be most prominent in the prostatic urethra, but, of course, they did not see the bladder so they did not really know. The trigone area was not visualized.

I think we should pause here and form some diagnostic opinion. Certainly there is no question that this patient had syphilis with central nervous system involvement. The main problem is to identify the palpable mass found on rectal examination. Several important points have been mentioned. The rectal mucosa over the mass was smooth, suggesting that the lesion itself was not primarily due to a rectal mucosal type of tumor. It did block urination (catheterization was necessary), which would point to involvement of tissues surrounding the bladder neck. The mass was fair-sized, and each examiner felt it, so there is no question about its presence. There is some question as to whether it involved the entire prostate; in one report it seemed to be a part of the upper border of the prostate, whereas the other report included the prostate and the entire mass as one feature. We know that cystoscopic examination was difficult, that at no time was the entire bladder visualized. So, there evidently was some involvement of the bladder mucosa. The prostatic urethra was elongated, again pointing to prostatic enlargement. The part of the bladder that was seen contained a cauliflowerlike mass.

One of the conditions to consider, of course, is a müllerian duct cyst, which is quite uncommon but nevertheless does occur; we have had two cases at Hines in recent years. One might ask how a müllerian duct cyst would mask something like this. It would be in the mid-line but probably would have a tremendous amount of inflammatory reaction around it. These cysts frequently do not manifest themselves until they have become inflamed. As a result, one may find quite a bit of induration and some inflammatory reaction around a müllerian duct cyst, which would be in the mid-line right at the upper border of

the prostate. The inflammatory reaction might give the impression that the mass involved not only the prostate but also the area above the prostate. In addition, there would be edema of the bladder mucosa of the trigone and bladder neck region that might make cystoscopic examination difficult. Inflammatory reactions of the bladder mucosa often simulate a primary tumor of the mucosa itself, so it is frequently necessary to do a biopsy to determine whether or not a tumor is present.

One might also consider an inflammatory reaction of the seminal vesicles. Neither seminal vesicle was palpable. This is normally the case, so that finding is not particularly significant. Nevertheless, a mass in this region—along the upper border of the prostate and involving the prostate—could be markedly inflamed seminal vesicles.

Another lesion one would have to consider, until x-rays and cystoscopic examination more or less ruled it out (but not completely), would be a large stone in the prostate.

Certainly the primary consideration, percentagewise, in a mass of this type is carcinoma, and the first order of business a biopsy.

An aspiration biopsy of the prostate reportedly did not reveal carcinoma. Such biopsies are not 100 per cent accurate, but the Turkel punch that we now use does give a fair percentage of accurate results if we feel fairly confident that we have a good representative specimen.

Because the patient had residual urine, a transurethral resection was done and 10 to 15 gm. of tissue removed from the floor of the urethra at the vesicle neck. In view of the difficulty in visualizing the trigone, one wonders where the cutting was done, but perhaps by this time localization was less difficult. The bladder neck tissue was reported as not malignant. Tissue removed from the prostatic urethra was reported as carcinoma, probably primary in the gastrointestinal tract, directing the line of investigation to that area.

Proctoscopic examination did not reveal a tumor in the lower part of the large bowel. A growth deep in the pelvis was palpable on rectal examination. An x-ray of the colon was negative except for irritable colon. Examination after a barium meal was essentially negative. Another barium enema evidently was given, and a filling defect was found in the mid-portion of the transverse segment—and probably the examining physicians felt this was the primary lesion. It appeared somewhat spastic, there was some irregularity of the mural border, and the colon was slightly dilated proximal to it. The examination was repeated, and the suspicious area filled completely this time and appeared normal. X-rays of the spine were negative for metastases. The gallbladder did not fill on x-ray examination. The patient was given x-ray and estrogenic treatment. Pyelonephritis developed and he died about six months after onset of acute obstruction in January.

We know that probably the most common types of colloid carcinomas are in the bowel. We have heard a great deal about the development of metastases, particularly from gastric carcinoma, to the rectal vesicle pouch (Blumer's shelf). Some types of Krukenberg tumors have shown this tendency to form drop metastases. It is felt that often the primary lesion has grown through the stomach wall and small tumor cells have fallen down in the peritoneal cavity to start growing on the peritoneum. About two or three times a year, in the genitourinary clinic, we encounter a case for consultation in regard to a definite palpable mass. Usually, investigation proves the presence of a primary tumor somewhere in the gastrointestinal tract. However, investigation in this case did not disclose any such primary tumor. It is possible, of course, that it was small enough to escape roentgenologic detection. Certainly, roentgenograms of the gastrointestinal tract are not infallible, even though they are successful in a high percentage of cases. Mention was made of a lesion in the mid-transverse colon, but on repeated study that area filled completely and the examining physicians seemed satisfied that it was normal. So the question of the tumor's origin arises. Was it in the rectum as a small, missed lesion? Was it in the stomach where also a small lesion was missed? Or could it have been primary within the bladder itself?

Opinions differ greatly as to the possibility

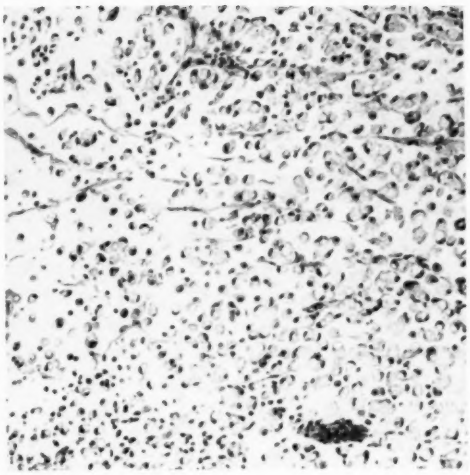

FIGURE 1. Mucin-forming signet-ring cells growing in a diffuse pattern with only a small amount of supporting stroma.

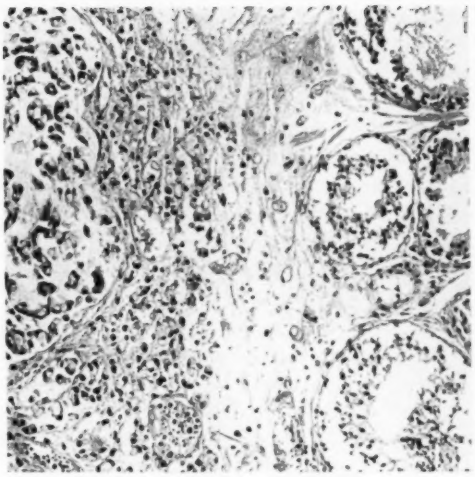

FIGURE 2. Cystitis glandularis with transition to mucin-forming signet-ring type of tumor cells. Area at right shows tumor growing in a glandular formation. Diffuse tumor is present in the stroma about this glandular area.

of colloid carcinoma arising as a primary entity within the bladder. Some workers deny that such an entity exists. Others even feel that adenocarcinoma as a primary lesion in the bladder is not a true diagnosis. At Hines, the percentage of adenocarcinomas in the bladder is about 1.12 per cent. Recently we collected a series of such cases, and I think the case under discussion fits in with that type of problem very well, inasmuch as no other primary could be found.

The question arises as to how transitional epithelium gives rise to adenocarcinoma, particularly colloid adenocarcinoma of the bladder. Various theories have been advanced. Some observers, of course, point to the fact that at one time during embryologic life the bladder and rectum were one, and to the possibility that some residual tissue of the rectal type within the bladder could result in this type of tumor.

Another possible site of origin is the urachus. Urachal tumors may have adenocarcinomatous changes and may even be colloid in type. However, the urachus is in the dome of the bladder leading up to the umbilicus, and one would expect a primary urachal tumor to be in that region rather than in the trigone and prostatic region.

Albarran, discussing the origin of bladder tumors, described the changes that take place with chronic infection and the irritation that accompanies it. There is hypertrophy of the tissue, and so-called papillary buds go down into the submucosa of the bladder—particularly the trigone, since it and the prostatic urethra are the areas most frequently involved in chronic infections. He described the small submucosal extensions as papillary projections, and they have been called Albarran's glands. There are really two types of these glands. One type gives rise to so-called benign prostatic hypertrophy. Most workers consider that benign prostatic hypertrophy, to some extent, actually is hypertrophy of the periurethral glands rather than of the prostate itself. It compresses the true prostate as a surgical capsule around the hypertrophy of the periurethral glands that have grown up.

Emmett at the Mayo Clinic found glands in the bladder, in the region of the trigone, which resemble rectal and large bowel-type mucosa. This is the second type of gland that Albarran described. Von Brunn also had his

name attached to the so-called papillary projections of transitional epithelium (Brunn's nests). It was felt that they actually were a metaplasia of transitional epithelium, that they could undergo either squamous metaplasia or metaplasia into adenomatous type of tissue. Chronic infection usually preceded the development of these nests, with cystic cystitis as a manifestation, and later they progressed to the squamous and adenomatous type of metaplasia. We do know that in cases of extrophia of the bladder there are mucus-secreting cells of the bladder mucosa. They have a tendency to form carcinoma. Some workers argue that even this change in bladder extrophia really is metaplasia due to chronic infection in the bladder. One might also say, however, that it was misplaced rectal entoderm as part of the congenital anomaly.

We have reviewed a number of cases in which autopsy was performed and in which a primary tumor was not found elsewhere in the body, so we feel that the entity of primary adenocarcinoma of the bladder not associated with the urachus is a very definite one. In these tumors, we have found both mucin-secreting and nonmucin-secreting cells. Neither type was particularly associated with the periurethral glands of the region of the trigone to the exclusion of the other type. In none of our cases was the tumor connected with the urachus. None of them acted like a primary lesion of the prostate; acid phosphatase values were normal in all the cases, and none of the tumors spread primarily to bone. We concluded that there is an entity of primary adenocarcinoma of the bladder, which could be colloid in type. Certainly, in view of the negative results of proctoscopic examination, intestinal and stomach roentgenograms, aspiration biopsy and x-rays of bone, this case would fit in with our series of primary adenocarcinomas of the bladder.

Discussion by Pathologists

DR. MELVIN C. GODWIN: From the autopsy slides it is clear that we are dealing with a mucin-producing adenocarcinoma. At autopsy, a tumor mass encircled the bladder neck completely and occluded the passage. The gastrointestinal tract was examined carefully and no tumor was found. There were no metastases. Other evidence of tumor could not be found. Microscopic examination of the tumor showed glands and diffusely growing mucin-forming cells, many of the signet-ring type, with little or no glandular pattern evident (figure 1). One area contained glandlike formations of cystic cystitis or cystitis glandularis which appear to show transitional stages in mucinous carcinoma formation (figure 2).

DR. KENNETH J. COSTICH: It seems to me there must have been cystitis for a long time, and I have never known of anyone establishing a connection between cystitis glandularis and a carcinoma which developed later. Would it not be possible to establish such a connection, perhaps, in this case?

DR. GODWIN: I do not believe that infection causes these tumors. I think it is the other way around—the tumor forms and infection follows. There probably is a relationship of adenocarcinoma to cystitis glandularis, at least in some cases. Here, biopsy did show what appeared to be benign glandular structures of cystitis glandularis in close association with mucinous carcinoma. However, investigators actually have searched for patches of mucin-forming cells in the bladder wall and failed to find them. Recently we had a biopsy specimen of bladder tissue that had mucin-forming columnar epithelium on the surface of the bladder—to my knowledge, the only instance of this finding. We have a basis right here for formation of the type of tumor discussed earlier. The potencies of bladder epithelium include the ability to form columnar epithelium with the capacity to produce mucin. No one questions squamous transformation in many areas (bladder, stomach, etc.) where malignant changes may develop. It takes more imagination to postulate mucinous adenocarcinoma by metaplasia, but the evidence appears to support this view.

Specialist Plus, Not Versus, Family Physician: A Setting Conducive to Effective Postgraduate Education

A. J. BAMBARA AND A. D. HUNT, JR.*

Hunterdon Medical Center, Flemington, New Jersey

To the members of the medical profession who have in some way heard of the Hunterdon Medical Center, its philosophic concept as it pertains to specialist-general practitioner relationships has been interesting, intriguing, exciting, and, to some, disturbing.

Many physicians may not have heard of this institution, and others may have some erroneous impressions about it. In order that a proper understanding of its principles may be obtained, we believed that an explanation was warranted. To this end, a specialist member of the hospital staff (A. D. H., Jr.) and a general practitioner (A. J. B.) who practices in the community will give their separate views on the subject.

A. J. BAMBARA

A. D. HUNT, JR.

As Seen by a Specialist

In rural and semirural areas, the general practitioner is, and will undoubtedly continue to be, the purveyor of medical care. In the free enterprise system which exists at present, physicians settle wherever financial success is most probable, and concentrations of population are essential for the success of specialists' practices. The diffuseness of the responsibilities of the general practitioner, however, makes it possible for him to have a busy practice in a thinly settled area. Although a few exceptions do exist in which groups of specialists operate in rural areas, there would seem to be little basis for predicting any fundamental change in the present situation.

The general practitioner in such an area is truly a family doctor, caring for all varieties of illnesses in all age groups, performing or not performing operations depending on the

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availability of referral sources. Of necessity he must have evening office hours, and a good night's sleep is a rarity. It is almost essential that his days off be spent in relaxing or cultural pursuits in order for him to be able physically and emotionally to carry on his grueling career. His opportunity to read medical literature is thus perforce seriously limited, and it is most difficult for him to deliver the kind of medical care which he would like to be able to deliver.

This problem is, of course, widely recognized by family physicians and medical educators alike, and has led to the development of many different postgraduate educational schemes, the most prevalent of which is the refresher course, in which the physician chooses a subject, pays a fee, and attends a series of lectures and clinics. The value of such courses is undoubtedly great. However, attendance at such courses is usually an elective matter, and the total percentage of physicians so doing must indeed be small. Furthermore, teaching is necessarily largely didactic and so lacks perhaps the most vital attribute in effective medical teaching; namely, the intimate and personal experience of managing patients in a setting where guidance, supervision and consultation are available.

If one be permitted to make the assumption, then, that the most effective technic in clinical teaching is guidance around the individual patient, a further assumption is justified; namely, that the ideal situation would be one in which the family physician, on a continuing long-term basis, had available guidance at a level comparable with that of a university.

Hunterdon Medical Center was founded with this concept in mind. A semirural county in which no hospital had previously existed, and in which no specialists had located, Hunterdon County, New Jersey, seemed an ideal area in which to conduct such an experiment in postgraduate education. It was reasoned that for an effective relationship between specialists and general practitioners to exist, both from the standpoint of delivering optimal medical care to the community and from that of good postgraduate education, competition between the specialists and the general physicians should be avoided. Thus it was established that the integrity of the general practitioner as a true family physician must be maintained. He would continue to practice medicine, pediatrics, minor surgery and uncomplicated obstetrics. The specialists would not practice in the traditional sense of the word, but would see patients on referral, would make house calls only on request of the family physician, and, in general, would assume a supportive and consultative role. The family physician staff member of the 120 bed hospital would be free to hospitalize his patients under his own care, maintaining the traditionally sound physician-patient relationship. The specialist chief of each service is responsible for the maintaining of university standards of medical care in his department and makes rounds daily with his house staff. In general, there are three categories of patients hospitalized at Hunterdon Medical Center.

First, there is the patient hospitalized by the family physician, and having an illness or condition which is within the general physician's scope to manage largely or totally on his own. Such patients are seen more or less casually by the chief of service on rounds. Progress is watched, but the ordering of studies and therapeutic measures, and formulations to the patients are the prerogative of the family doctor. Nearly all of these patients, however, become the subject of informal discussion between specialist and general practitioner, such "curbstone" consultations being highly enlightening for all concerned.

Second, there is the patient whose basic management remains in the hands of the family physician, but in the care of whom he feels the need for formal consultation. In this situation, careful and complete examination of the patient is made by the specialist, and his findings are incorporated in the chart. An appropriate consultation fee is charged to the patient. From the time of the request for consultation until the time of the patient's dismissal from the hospital, the family physician and specialist collaborate closely in the management of the patient. Such a relationship between family doctor and specialist, who work intensively together in the management

of a difficult medical problem, in our opinion provides the opportunity for the most effective type of postgraduate education.

Third, either because of distance of the hospital from the doctors' offices, or because of extraordinary complexity of the cases involved, there are some patients who are referred to the hospital, to be under the complete care of one of the specialist staff. Under such conditions, the learning experience is less intense, but telephone calls describing the findings and progress, together with a complete typed report of the patient's course and the recommendations serve in some measure to insure that the referring physician profits maximally from the hospitalization of his patient. Furthermore, during such a hospitalization, the referring physician usually comes in periodically, talks with the patient, and discusses the problem with the specialist, so that in many instances the close personal relationship is maintained.

A word must be said regarding major surgery, both general and special. It is Medical Center policy that major operations are performed only by qualified specialists who meet the requirements for appointment to the faculty of New York University. Thus, all patients requiring major surgical procedures are referred to the appropriate specialists. Again, however, the family physicians visit their patients, discuss them with the surgeons, and assist at operations if they so desire.

Members of the house staff prepare the histories and make the physical examinations in all cases in which patients are admitted to the hospital. This house staff is composed of interns rotating from one or two New York hospitals, specialty residents similarly rotated, residents in general practice at Hunterdon Medical Center, and senior medical students from three medical schools. The eager freshness of the typical house officer has its usual effect in keeping both family physicians and specialists "on their toes," and, in turn, we believe that the close association with men on the "front lines" of medical practice is a warming and enriching experience for house officers and students which is hard to duplicate.

Frequent departmental and general staff conferences, clinicopathologic conferences in which cases are discussed by the family physicians, and special meetings featuring outside speakers comprise a vigorous and well-rounded formal educational program.

The specialist staff consists of the following full-time members: three internists, a general surgeon, an otolaryngologist, an obstetrician and gynecologist, a pathologist, an anesthesiologist, a psychiatrist, a radiologist, an ophthalmologist, an orthopedic surgeon and a pediatrician. Part-time members include a urologist and consultant in physical medicine and rehabilitation. Consultants in dermatology, allergy, neurology, neurosurgery and other fields are available either on a regular schedule basis or as needed. All services are charged to the patients, and the fees are paid into the professional service fund. All chiefs of service receive an identical income from this fund, and assistants and part-time members are paid proportionately. After two years of operation, the group is solvent, and the trend is toward financial success. Considerable aid in the form of grants from the Commonwealth Fund and the Kress Foundation made possible the establishment of such a large and complete medical group.

All members of the full and part-time specialist staff hold faculty appointments at New York University-Bellevue Medical Center, and, for the most part, spend a certain amount of time in the city in teaching or research activity. Thus, for the specialist, this setting provides an opportunity to combine the delivering of university-type medical care with country living, to participate in resident and undergraduate training, and to collaborate in that most important of all pedagogic activities, namely, postgraduate medical education.

We believe that, by maintaining and supporting the integrity of the family physician, by establishing a close collaborative relationship between specialist and general practitioner, and hence by bringing first-class medical care to a rural community, we have demonstrated again that private medicine can work in the best interest of the people, and that an effective blow may have been struck against the advocates of socialized medicine.

As Seen by a Family Physician

Because Hunterdon Medical Center is considered unique in its concept, it has received its share of publicity. In some of its individual features I am sure it compares with other institutions. But in its totality, it is singular in that it answers the difficult problem of bringing more than merely adequate medical care to a rural community and at the same time raising the educational standards of the general practitioner who is urged, encouraged, and convinced that he should belong to the staff and take care of his own patients according to his ability and qualifications.

As a general practitioner member of the team, I (A. J. B.) should like to break down the last statement into its component parts, keeping in mind that my point of view will be slanted toward the aspect of how this new type of organization has affected and is affecting me, a general practitioner.

First, in an attempt to render more than just adequate medical care, the hospital is staffed by a group of specialists who have been well trained in their respective fields, and is composed solely of "Board" men. That the staff could have been just as proficient if the members were not American Board members is irrelevant. These men have brought with them a university-type medical attitude that has not been available before. That this is claimed to be somewhat better than average can not be contested. This is not to be interpreted as an attempt to disparage any of the fine men who gave the people and doctors of Hunterdon County the benefit of their skill, sympathetic understanding, kind consideration and wholehearted cooperation before the medical center opened.

The second portion of my statement, "rural area," needs clarification. My practice is located in Hunterdon County, which is the largest county geographically in the state of New Jersey and is centrally located within the state. It covers about 400 square miles and has a population of about 43,000. From my part of the county, my patients traveled from 15 to 50 miles to be hospitalized in hospitals located in six different directions, since no hospital was available in the county. Needless to say, because of distance, I was unable to attend patients who were in hospitals farther than the closest one, even had I been allowed to do so. At the present time, very few go anywhere but to the Hunterdon Medical Center. While Hunterdon County was at one time seated at the low end of the table from which it was being served satisfactory medical care, it now has assumed a higher place at the banquet table of health and is serving medical care of the highest caliber. The last has become first.

Without a doubt, this medical center is serving a definite need to the individual patient, who now does not have to travel far, and to the community in general. A need directed toward the general practitioner brings me to the third part of my statement; namely, the raising of the educational standards of the general practitioner in a rural community.

For the doctor who is sincere and desires to further his postgraduate training, there are certainly places where he can go and things he can do. However, a physician in a rural community is usually busy, and it means making an extreme effort to get away.

The coming of a specialist staff whose qualifications have been approved by a recognized teaching institution has brought the knowledge of the latest in medical developments to a small country hospital which serves a comparatively large geographic area. The mere presence of such men has been intellectually stimulating. I have found myself going back to my books more often than before. My former excuse of not having the time to read medical journals has been supplanted by the desire to be able to hold up my side of a medical discussion. This, of course, is nothing more than sheer pride, which I rationally describe as justifiable pride. I am sure that more of us (rural general practitioners) can profit by such incentive.

It is now not unusual for me to stop one of the specialists in the hospital corridor to ask him for help on a particular problem. Or I might call him on the telephone to get an answer in a hurry, while the patient is sitting in my office. While walking through the hospital

halls I have found myself preoccupied with a particular problem. The realization that a well-stocked library is readily available has influenced me in immediately seeking the answer while the problem is still fresh in my mind. I find that the interns also are a source of education for me. The questions they ask, the things they do, the need for explaining my attitude toward certain standards of treatment, all tend to stir up a stagnant pool of information. Facts I had forgotten come to mind again; new knowledge is acquired.

Some of the departments hold weekly conferences for the intern training program which I have attended when I have had the opportunity. Our monthly clinicopathologic conferences have in the main been conducted by the general practice members of the staff, except when we have felt the need for an occasional change. I was nervous when it was my turn, but I considered it a tremendous experience.

This institution provides a place where the G.P. is considered an important member of a team in treating patients, has a voice in policy making regarding medical practice by virtue of his equal representation on the medical board, can have access to the Board of Trustees through a purposely established liaison, and can complain to the director, superintendent, specialist—in fact to any one—and be heard. He can attain all this by showing he is suitably qualified both professionally and morally without having to submit to a waiting period to prove himself. This concludes the explanation of my initial statement.

As in all things, there are two sides to every story. To give the impression that there have been no "bugs" and that there will be none would not be completely true or honest. There have been a few problems, some involving medical policy, some ethics, some personality conflicts. But in each instance the G.P. staff has been adequately represented and has participated actively in the discussions. It may be said that the union between the specialist staff and the general practitioner staff of Hunterdon Medical Center appears to be a happy one, since both groups bring their differences out in the open where free discussion, reasoned judgment, and a charitable attitude toward the rights and opinions of others tend to make for peace and harmony.

In summary, then, my own reasons for valuing the existence of the Hunterdon Medical Center are:

1. I can take care of my own patients up to reasonable limits—the patients' welfare having first consideration.

2. I can avail myself of continuous specialist supervision for my patients.

3. I can obtain additional postgraduate knowledge without the need of leaving my practice.

4. I have a voice in formulating medical policy through proper representation.

5. I have a happy place in which to work.

Editorials

Postgraduate Medicine

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Public Health and Preventive Medicine in Everyday Practice

JOHN A. KOLMER*

Achievements

PREVENTIVE medicine, which starts with the fetus in utero and continues throughout the remainder of life, always has been and still is the most important goal in man's fight against disease. Effective preventive measures do not always demand a complete understanding of the etiology of a disease since certain known links in its pathogenesis may be broken.

The crude mortality rate of 17.2 per 1000 individuals of 50 years ago has now been reduced to about 9.2 per 1000 (a decrease of 46 per cent). During this period there has been an 80 per cent decline in mortality per 1000 infants under one year of age. If the mortality rates of 1900 prevailed today there would be more than 1,500,000 additional deaths per year. Future declines in mortality rates will depend largely on progress in reducing deaths due to heart disease and cancer.

In 1900 the life expectancy of white males was about 50 years and about 54 years for white women, with about 16 years less in Negroes of both sexes. Today the life expectancy of white males is about 68 years and about 73 years in white women, with about 7 years less in Negroes of both sexes.

Everyday Practice

The major functions of departments of health are the control of communicable diseases and education of the laity in relation to health. Practicing physicians should not only utilize these facilities but also advise, *constructively* criticize and actively participate in these activities through their local and state medical societies. In rural areas it is particularly important for practicing physicians also to co-

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Abstract of an address given by invitation before the Georgia Public Health Association, May 29, 1956.

operate, lead and advise all local groups and agencies concerned with educational activities and community improvements in relation to the conservation of health.

Of equal importance is the fact that practicing physicians are in strategic position to advise patients not only on the prevention of many diseases but also on the prevention of complications or sequelae or both. Although practicing physicians are mainly concerned with the diagnosis and treatment of diseases, these preventive measures constitute a highly important phase of the daily practice of medicine which cannot be assumed by departments of health.

Active Immunization

Active immunization or vaccination is effective in preventing cholera, diphtheria, epidemic typhus fever, influenza, oriental sore, pertussis, Q fever, rabies, Rocky Mountain spotted fever, smallpox, tetanus, typhoid-paratyphoid fevers and yellow fever.

Fortunately the Salk vaccine is now known to be safe and of promising value in preventing at least paralytic types of poliomyelitis.

The efficacy of BCG vaccination of tuberculin-negative individuals is still under evaluation but appears to be warranted, especially in children and adults unavoidably exposed to open cases of pulmonary tuberculosis.

Immunization against influenza is valueless during epidemics and hardly feasible for whole populations.

Practicing physicians are particularly responsible for immunization of infants and preschool children against diphtheria, pertussis, poliomyelitis, tetanus and smallpox.

Passive Immunization

Antitoxins are effective in preventing botulism, diphtheria and tetanus. Diphtheria and tetanus antitoxins are especially indicated for exposed children and adults who have not been vaccinated or revaccinated against these diseases. Antitoxins, however, should not be administered, or should be given only with special precautions, to individuals known to have or suspected of having asthma due to allergic sensitization to horses.

Human gamma globulin is of value in the modification or prevention of measles, German measles, infectious hepatitis and poliomyelitis. However, it is advisable for physicians not only to avoid immunizing female children and adolescents against German measles whenever possible, but also actually to encourage their exposure to the disease with the hope that they will contract it and thus acquire immunity as a safeguard against its occurring during pregnancies, with subsequent danger of infants being born with various congenital defects.

Chemoprophylaxis

Penicillin and sulfadiazine have proved effective in the prophylaxis of group A beta hemolytic streptococcal infections, such as erysipelas, nasopharyngitis, puerperal endometritis, scarlet fever and tonsillitis, as well as in the prevention of primary and recurrent glomerulonephritis, rheumatic fever and carditis. Penicillin is preferred and may be administered by the oral route in the prevention of streptococcal sore throat and recurrent rheumatic fever and carditis. Otherwise intramuscular injections are preferred. Tetracycline antibiotics should be employed in individuals with natural or acquired allergic sensitization to penicillin, and for the prevention of psittacosis. Oxytetracycline (TERRAMYCIN®) should be administered orally for the prophylaxis of Q fever. Sulfadiazine is usually preferred in the prophylaxis of bacillary dysentery, bubonic plague and meningococcal meningitis.

Penicillin is also of value in the prophylaxis of subacute bacterial endocarditis in cases of congenital and valvular heart disease and in the prevention of pyogenic infections in diabetics following extractions of infected teeth, tonsillectomies, etc. Intramuscular injections should be given before, after, and on the following one or two days. Penicillin is effective in the prophylaxis of gonorrhea in adults of both sexes but may mask syphilis; it is also useful in the prophylaxis of gonococcal vulvovaginitis of children. Penicillin administered intramuscularly is also effective in preventing acquired syphilis, although total dosages comparable to those employed in treating primary

syphilis are required. In syphilitic women adequate penicillin therapy during the first and second trimesters of pregnancy practically insures the birth of nonsyphilitic infants.

Since the oral administration of isoniazid has been found effective in the prophylaxis of experimental tuberculosis of guinea pigs (Palmer and Ferebee), it appears worthy of trial in the prevention of human tuberculosis.

Periodic Health and Screening Examinations

Periodic health examinations are primarily for the early detection of diseases and especially those of major importance in relation to disabilities and longevity, such as cancer, cardiovascular diseases, diabetes mellitus, nephritis, obesity, malnutrition, pulmonary tuberculosis, syphilis, etc. They are also of great value in promoting health and especially when accompanied by counseling in relation to work, diet, alcoholic beverages, smoking, sleep, exercise, recreation, socio-economic conditions, etc. Consequently physicians should not regard periodic health examinations as unnecessary, trivial or boring but as opportunities for teaching patients that it pays to keep fit and well as long as possible.

While mass screening by clinical, x-ray and laboratory examinations for anemias, cancer, cardiovascular diseases, defective vision (including glaucoma), defective hearing, diabetes mellitus, obesity, physical impairments, pulmonary tuberculosis and syphilis does not necessarily establish diagnosis it is usually of value and especially when combined with case follow-ups. Furthermore, it is of value in relation to community health education and merits the cooperation of local medical societies as well as of individual physicians.

Focal Infection

Focal infection as a possible cause of ill health is no longer a theory but is firmly established in both medicine and dentistry. Primary foci may be circumscribed or diffuse, acute or chronic, single or multiple. Their detection frequently requires considerable skill and experience. Secondary conditions and diseases which may be due to direct mucosal continuity, transient bacteremias, absorption of toxins, or acquired allergic sensitization to the soluble products of bacteria include not only subacute bacterial endocarditis and the infective arthritides, but also some of the fibrositides, pyodermias, and infections of the lower respiratory tract, kidneys, eyes and brain. Many individuals escape illness, at least temporarily, due to natural or acquired resistance, escape from acquired allergic sensitization, or the absence of other factors favoring the development of secondary diseases. Physicians should insist on periodic dental care for adults and for children three years of age or older, and, whenever possible, also on the prevention of caries and the eradication of primary foci of infection of dental or other location. This requires sound clinical judgment in order to avoid the needless extractions of teeth, tonsillectomies, adenoidectomies, etc.

Coronary Atheromatosis

The exact etiology of coronary atheromatosis is still not known. In many instances there seems to be a familial or hereditary predisposition to the disease. These individuals particularly require periodic examinations and advice. Early detection and adequate treatment of diabetes mellitus, essential hypertension, hypothyroidism and syphilis are important, as are the correction of obesity and maintenance of normal weight in relation to sex, age and height. Reduction or elimination of animal fats in diet, with total fats not exceeding 20 to 25 per cent of the total calorie intake per day, may be of value. Oophorectomies should be avoided as much as possible, as should overwork, excessive anxiety, nervous tension and excessive smoking. There should be moderate physical activity with adequate rest and recreation. Prolonged anticoagulant therapy may be helpful in preventing subsequent attacks of coronary thrombosis when dosage is controlled by frequent prothrombin time determinations.

Benign Essential (Primary) Hypertension

The exact etiology of essential hypertension is still unknown. In many instances there ap-

pears to be a familial or hereditary predisposition to the disease. These individuals, too, require periodic examinations and advice, with correction of obesity and maintenance of normal weight in relation to sex, age and height. Early detection and adequate treatment of diabetes mellitus are important, as are prompt detection and surgical removal of pheochromocytoma of the adrenal glands. There should be no excessive use of sodium chloride in foods; patients should avoid overwork, excessive anxiety and nervous tension and have adequate rest and recreation. The physician should follow common-sense management with alleviation of excessive fear and the teaching of patients that they may live long, comfortable and useful lives if they learn to live with and respect their limitations.

Congestive Heart-failure

The preventive aspects of congestive heart-failure depend primarily on early diagnosis and adequate treatment of heart diseases with special reference to primary and recurrent rheumatic carditis, hypertensive and coronary arteriosclerotic heart disease, myocardial infarction, syphilitic aortitis, cor pulmonale, severe arrhythmias and pericarditis. There should be early diagnosis and adequate treatment of hyperthyroidism, myxedema, severe anemias and severe thiamine (vitamin B_1) deficiencies, and prevention of subacute bacterial endocarditis in congenital and valvular heart diseases.

Whenever possible, operation should be performed for correction of congenital heart disease and coarctation of the aorta. Physicians should guide adolescents and adults with valvular and congenital heart diseases in relation to strenuous exercise, sports and physical work, for the conservation of adequate cardiac reserve as long as possible. Also, the physician can help to prevent iatrogenic heart disease and functional heart disorders by avoiding ill-considered remarks, acts and errors.

Cancer

While the complete etiology of cancer is still unknown, the following preventive measures appear to be sensible and advisable: (1) avoidance of excessive smoking in relation to cancer of the lips, tongue, buccal mucosa, larynx, lungs and, possibly, of the esophagus; (2) avoidance and correction, or both, of chronic irritations and ulcerations of the oral cavity, cervix, gallbladder (calculi), urinary bladder (calculi) and kidneys (calculi and chronic infections); (3) avoidance of chronic trauma of the breasts of women and the encouragement of early marriage and breast feeding; (4) avoidance of soot, coal tar, pitch, diesel engine gases, isopropyl alcohol, asbestos, chromates, arsenic, nickel, radioactive dusts and other carcinogens in relation to cancer of the lungs and skin; (5) avoidance of excessive exposure to sunlight, ultraviolet and ionizing radiations in relation to cancer of the skin and internal organs; (6) avoidance of consanguineous marriages in relation to hereditary predisposition to retinoblastoma; (7) correction of oral leukoplakia in relation to cancer of the mouth; (8) correction of vaginal leukoplakia, kraurosis and Bowen's disease in relation to carcinoma of the vagina; (9) correction of syphilitic glossitis in relation to cancer of the tongue; (10) correction of phimosis in relation to cancer of the penis; (11) orchiopexy in relation to cancer of the testes; (12) removal of papillomas of the vocal cords in relation to cancer of the larynx; (13) removal of colonic polyps in relation to cancer of the colon; (14) removal of adenomas of the thyroid gland in individuals under 60 years of age; (15) removal of hydatidiform moles in relation to cancer of the uterus.

Obesity

Obesity predisposes to diabetes mellitus, hypertension, arteriosclerosis, chronic nephritis, myocardial failure, osteoarthritis, orthopedic foot troubles, varicose veins, menstrual disorders, postsurgical complications, accidents, psychoneuroses and suicides. Furthermore, it usually reduces longevity at all ages in both sexes. Prevention should start in childhood. Overeating is the cause of obesity in about 94 per cent of cases. Heredity, pregnancy, the menopause and sedentary habits are contributory etiologic factors. Hypothyroidism and other hormonal imbalances are seldom involved. Physicians and dentists should

always explain the potential dangers of obesity to their patients, advise weight reduction, encourage those of normal weight to keep it so, support public health and other agencies in educational programs, and set good examples themselves. They should also fight weight-reducing fads and fakes and develop the patient's responsibility in securing and maintaining approximately normal weight in relation to age, sex and height.

Diabetes Mellitus

Diabetes mellitus may be due to diseases of the pancreas or disorders of endocrine glands resulting in hypoinsulinism. Otherwise the exact etiology is still unknown, although hereditary predisposition, obesity, and the excessive ingestion of sugar are important contributory factors. The incidence of diabetes mellitus in any locality is in direct ratio to the frequency with which practicing physicians, clinics and hospitals employ fasting or postprandial (preferred) blood glucose tests for its detection, since urine examinations alone are totally inadequate to detect early and mild asymptomatic cases of the disease. In this connection mass screening surveys are of value. In view of the etiologic importance of heredity, diabetic males and females and those of diabetic families should not intermarry. Individuals with renal glycosuria should be placed on carbohydrate-restricted diets and carefully watched for the possible development of diabetes mellitus. Otherwise preventive measures are practically confined to those for avoiding obesity and excessive consumption of sugar. Such potentially dangerous complications as ketosis, acidosis and coma, coronary atheromatosis, peripheral arteriosclerosis, retinopathy, neuropathy, furuncles, carbuncles, pulmonary tuberculosis, infections of the kidneys, renal papillary necrosis, intercapillary glomerulosclerosis and hydramnios during pregnancy with fetal deaths can be prevented only by early detection and adequate treatment of the disease.

Peptic Ulcer

Apparently peptic ulcer is due to the excessive secretion of hydrochloric acid and pepsinogen by the gastric mucosa, probably in association with diminished secretion of protective mucus. The exact etiology of these changes, however, is still obscure. Familial predisposition may be a factor in some cases. Others may be due to chronic emotional conflicts and stresses in tense, hard-working, overly conscientious and worrisome individuals, resulting in central overstimulation of the vagus nerves and increased production of ACTH and adrenocortical steroids. Under the circumstances the physician can only endeavor to correct the emotional conflicts and stresses and to caution against overwork with inadequate rest and recreation and excessive smoking, especially of cigarettes.

Accidents and Poisonings

The appalling incidence and mortality rates of accidents and poisonings at all ages over one year demand that every physician and surgeon be a crusader for their prevention in the everyday practice of medicine. Indeed, the incidence of accidental poisonings of children with crippling effects exceeds that of poliomyelitis. Consequently all physicians and surgeons should be "accident minded" and never pass up opportunities for giving advice and instructions whenever possible. This is particularly valuable in connection with the distribution of printed instructions which should be available in the waiting rooms not only of pediatricians but also of all general practitioners and specialists. Homes should be inspected at least occasionally in relation to the storage of *all medicines*, caustics, cleaning agents, floor and fingernail polishes, insecticides, lead toys and paints, etc., and in relation to electric outlets, fire hazards, floors and steps, the use of ladders, and other sources of accidents. Backyards should also be inspected for broken glass, wooden stakes, nails, sharp tools, etc.

About 93 per cent of general practitioners are in strategic position to advise against the hazards of occupational diseases with special reference to farms and small industries. Although large industries usually provide adequate facilities for accident and sickness prevention, supplementary advice and instructions

given by practicing physicians are of great value. Needless to state, practicing physicians are likewise in strategic position to reduce the appallingly high and constantly increasing incidence of motor vehicle accidents by advising and cautioning teen-agers and adults of both sexes in relation to the dangers of alcoholism, speeding, infringement of traffic regulations, etc., and at least to attempt the correction of "accident proneness" due to fatigue, carelessness, indifference, emotional apathy and other psychiatric disturbances. All physicians, surgeons and dentists also have an important personal responsibility in preventing the transmission of homologous serum hepatitis which requires the thorough sterilization of needles, syringes, etc. by heat since the virus is unusually resistant to destruction.

Addictions

Undoubtedly "an ounce of prevention" is worth infinitely more than "a pound of cure" insofar as addictions are concerned. In view of the many and potentially serious evils of chronic alcoholism, physicians should guard themselves against this addiction, cooperate with all agencies concerned in its prevention and embrace every opportunity to advise and warn teen-agers and adults of both sexes in everyday practice. Physicians should also not only guard themselves against narcotic addictions and cooperate with all agencies concerned in their detection and prevention, but exercise great care in administering opium, morphine, heroin, DEMEROL® and codeine for the relief of pain. The administration of narcotics is warranted, however, for the relief of severe intractable pain in incurable diseases (i.e., some cases of cancer), since patients usually do not live long enough to make possible addiction a matter of importance. Physicians should also exercise caution in prescribing barbiturates and always endeavor to detect and correct the causes of sleeplessness in order to reduce the prescribing of potentially dangerous hypnotics to an absolute minimum. Caution is also required in prescribing amphetamines for the appeasement of appetite and hunger in weight reduction and the relief of fatigability, since patients may acquire addictions because of the euphoric effects of these compounds.

Geriatrics

Since the population increase of individuals over 65 years of age is now about five times higher than the increase of the population in general, the preventive aspects of ill health in the aged have become increasingly important. Unfortunately, public health efforts in this direction have been meager and the problem has become increasingly important in relation to the everyday practice of medicine. The health problems of the aged are due much more to mental than to physical disturbances. Enforced idleness with loss of companionship and dignity, insecurity and socio-economic problems, and problems arising from a lack of emotional adjustment to lonesomeness, family neglect, etc., are of primary importance. Practicing physicians should always discuss the possible problems confronting those approaching economic idleness one or more years in advance with the hope of being able to offer valuable advice and guidance if and when necessary or advisable.

It is particularly important that physicians stress the need of aged individuals to keep mentally and physically occupied within their limitations in order to avoid the evils of enforced mental and physical idleness as long as possible. Periodic health examinations are advisable, with the provision of proper spectacles, good lighting, hearing aids or training in lip reading, comfortable dentures, etc. Aged persons should remain in their own homes as long as possible, husbands and wives should not be separated, friendships with younger persons should be encouraged, increased precautions should be taken against home accidents, and relatives should be advised of the evils of neglect and lack of love and sympathy.

Program

41st Interstate Postgraduate Medical Assembly

Cleveland, Ohio — October 22–25, 1956

Program Schedule

Monday, October 22, 8:25 A.M.

8:25 Welcome:
A. Macon Leigh, M.D., President, Academy of Medicine of Cleveland and Cuyahoga County Medical Society.

8:30 Clinic: The Management of Traumatic Face Injuries.
Donald M. Glover, M.D., Clinical Professor of Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.

9:00 Address: Urinary Tract Infections—The Necessity for Teamwork.
Paul S. Rhoads, M.D., Professor of Medicine, Northwestern University Medical School, Chicago, Illinois.

9:30 Clinic: Preoperative Evaluation for Major Surgery.
Robert M. Zollinger, M.D., Professor and Chairman of the Department of Surgery, Ohio State University College of Medicine, Columbus, Ohio.

10:00-11:00 *Intermission for Review of Exhibits*

11:00 Clinic: New Treatments for Rheumatoid Arthritis.
William H. Kammerer, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College, New York, New York.

11:30 Address: Indications and Contraindications of Hysterectomy.
John C. Burch, M.D., Professor of Gynecology, Vanderbilt University School of Medicine, and Gynecologist at Vanderbilt University Hospital, Nashville, Tennessee.

Noon Intermission

1:30 P.M.

1:30-2:30 Panel: Gastrointestinal Bleeding.
William D. Holden, M.D., Oliver H. Payne Professor and Director of the Department of Surgery, Western Reserve University School of Medicine, Cleveland, Ohio, Moderator.
Joseph B. Kirsner, M.D., Professor of Medicine, University of Chicago School of Medicine, Chicago, Illinois.

Alton Ochsner, M.D., Professor of Surgery, Tulane University School of Medicine; Director of Surgery, Ochsner Clinic and Ochsner Foundation Hospital, New Orleans, Louisiana; President, Interstate Postgraduate Medical Association of North America.

Hymer L. Friedell, M.D., Professor of Radiology, Western Reserve University School of Medicine; Director of Radiology, University Hospitals of Cleveland, Cleveland, Ohio.

2:30-3:00 *Intermission for Review of Exhibits*

3:00 Address: Signs and Symptoms of Anxiety Tension States.
Marc J. Musser, M.D., Professor of Medicine, University of Wisconsin Medical School, Madison, Wisconsin.

3:30 Address: The Problem of Ulcerative Colitis.
Joseph B. Kirsner, M.D., Professor of Medicine, University of Chicago School of Medicine, Chicago, Illinois.

4:00-4:30 *Intermission for Review of Exhibits*

4:30 Address: Clinical Significance of Polyps of the Rectum and Colon.
Rupert B. Turnbull, M.D., Department of Surgery, Cleveland Clinic, Cleveland, Ohio.

5:00 Address: Chronic Relapsing Pancreatitis.
Kenneth W. Warren, M.D., Department of Surgery, Lahey Clinic, Boston, Massachusetts.

Evening Program

7:30 P.M.

7:30 Address: The Influence of Nutritional Processes on Aging.
Tom D. Spies, M.D., Director, Nutrition Clinic, Hillman Hospital, Birmingham, Alabama; Professor and Head of the Department of Nutrition and Metabolism, Northwestern University Medical School, Chicago, Illinois.

8:00-9:00 Panel: Jaundice.
Robert M. Zollinger, M.D., Professor and Chairman of the Department of Surgery, Ohio State University College of Medicine, Columbus, Ohio, Moderator.

Kenneth W. Warren, M.D., Department of Surgery, Lahey Clinic, Boston, Massachusetts.

Harry Goldblatt, M.D., Pathologist, Mount Sinai Hospital of Cleveland, Cleveland, Ohio.

Warren E. Wheeler, M.D., Professor of Pediatrics and Bacteriology, Ohio State University College of Medicine, Columbus, Ohio.

Everett N. Collins, M.D., Cleveland Clinic, Cleveland, Ohio.

Tuesday, October 23, 8:00 A.M.

8:00 Address: Present Status of Hormone Therapy in the Treatment of Breast Cancer.
Mortimer B. Lipsett, M.D., Clinical Assistant, Medical Service, Memorial Hospital; Instructor in Medicine, Cornell University Medical College; Assistant, Sloan-Kettering Institute, New York, New York.

8:30 Address: The Diagnosis and Management of Placental Insufficiency.

Allan C. Barnes, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, Western Reserve University School of Medicine, Cleveland, Ohio.

9:00 Address: The Treatment of Congenital and Traumatic Deformities.

Claire L. Straith, M.D., Straith Clinic—Plastic Surgery—Detroit, Michigan.

9:30 Address: Hypophysectomy in the Vascular Complications of Diabetes.

Edgar S. Gordon, M.D., Professor of Medicine, University of Wisconsin Medical School, Madison, Wisconsin.

10:00-11:00 *Intermission for Review of Exhibits*

11:00 Clinic: Recurrent Operations of the Biliary Tract.

Richard B. Cattell, M.D., Director, Lahey Clinic; Surgeon-in-Chief, New England Baptist Hospital; Surgeon, New England Deaconess Hospital, Boston, Massachusetts; Past President, Interstate Postgraduate Medical Association of North America.

11:30 Address: What Can Be Learned by Antibiotic Sensitivity Testing.

Warren E. Wheeler, M.D., Professor of Pediatrics and Bacteriology, Ohio State University College of Medicine, Columbus, Ohio.

Noon Intermission

1:30 P.M.

1:30 Clinic: The Painful Shoulder.

Anthony F. DePalma, M.D., James Edwards Professor of Orthopedic Surgery and Head of the Department, Jefferson Medical College, Philadelphia, Pennsylvania.

2:00 Clinic: Benign Lesions of the Colon.

Warren H. Cole, M.D., Professor of Surgery and Head of the Department, University of Illinois College of Medicine, Chicago, Illinois; Past President, Interstate Postgraduate Medical Association of North America.

2:30-3:00 *Intermission for Review of Exhibits*

3:00 Address: The Management of Benign Lesions of the Lower Esophagus.

Paul Nemir, Jr., M.D., Associate Professor of Surgery, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pennsylvania.

3:30 Address: Suspicion of Poison or Foul Play as the Cause of Death.

Alan R. Moritz, M.D., Professor of Pathology and Director of the Institute of Pathology, Western Reserve University School of Medicine, Cleveland, Ohio.

4:00-4:30 *Intermission for Review of Exhibits*

4:30 Address: Total Care of Patients With Severe Paralysis.

Vernon L. Nickel, M.D., Assistant Clinical Professor of Orthopedic Surgery, College of Medical Evangelists School of Medicine, Los Angeles, California.

5:00 Address: Red Cell Survival Studies in the Management of Hematologic Problems.

Malcolm Brown, M.D., Professor of Medicine, Queen's University, Kingston, Ontario, Canada.

Evening Program

7:30 P.M.

7:30 Address: Sleep Problems in the Early Years.

Benjamin Spock, M.D., Visiting Professor of Child Development, Western Reserve University School of Medicine, Cleveland, Ohio.

8:00 Attendance Awards.

8:15-9:15 Panel: Thyroid Disease.

Warren H. Cole, M.D., Professor of Surgery and Head of the Department, University of Illinois College of Medicine, Chicago, Illinois; Past President, Interstate Postgraduate Medical Association of North America, Moderator.

Richard B. Cattell, M.D., Director, Lahey Clinic; Surgeon-in-Chief, New England Baptist Hospital; Surgeon, New England Deaconess Hospital, Boston, Massachusetts; Past President, Interstate Postgraduate Medical Association of North America.

Edgar S. Gordon, M.D., Professor of Medicine, University of Wisconsin Medical School, Madison, Wisconsin.

Hymer L. Friedell, M.D., Professor of Radiology, Western Reserve University School of Medicine; Director of Radiology, University Hospitals of Cleveland, Cleveland, Ohio.

Wednesday, October 24, 8:00 A.M.

8:00 Address: Tranquilizing Agents for Nervous Disorders in General Practice.

F. Garm Norbury, M.D., Medical Director, The Norbury Sanatorium, Jacksonville, Illinois.

8:30 Clinic: Injuries of the Hand.

Michael L. Mason, M.D., Professor of Surgery, Northwestern University Medical School, Chicago, Illinois.

9:00 Address: Hyperventilation Syndromes: Clinical and Physiologic Observations.

Bernard I. Lewis, M.D., Associate Professor of Medicine, State University of Iowa College of Medicine, Iowa City, Iowa.

9:30 Address: The Basic Principles of Gastric Surgery.

George Crile, Jr., M.D., Department of Surgery, Cleveland Clinic, Cleveland, Ohio.

10:00-11:00 *Intermission for Review of Exhibits*

11:00 Clinic: The Painful Wrist.

James K. Stack, M.D., Associate Professor of Orthopedic Surgery, Northwestern University Medical School, Chicago, Illinois.

11:30 Clinic: Carcinoma of the Stomach.
Alton Ochsner, M.D., Professor of Surgery, Tulane University School of Medicine; Director of Surgery, Ochsner Clinic and Ochsner Foundation Hospital, New Orleans, Louisiana; President, Interstate Postgraduate Medical Association of North America.

Noon Intermission

1:30 P.M.

1:30 Address: Cancer of the Vulva.
John Parks, M.D., Professor of Obstetrics and Gynecology, The George Washington University School of Medicine, Washington, D.C.

2:00 Address: Large Bowel Obstruction Following Pregnancy.
E. Bruce Tovee, M.D., Associate Surgeon in the Department of Surgery, University of Toronto; Senior Surgeon, Toronto General Hospital, Toronto, Ontario, Canada.

2:30-3:00 *Intermission for Review of Exhibits*

3:00 Address: Drug Therapy in Hypertension.
Irvine H. Page, M.D., Director of Research, Cleveland Clinic Foundation, Cleveland, Ohio.

3:30 Address: Eczematoid Conditions of the Hands.
Francis Eugene Senear, M.D., Assistant Professor of Pediatrics, Northwestern University Medical School, Chicago, Illinois.

4:00-4:30 *Intermission for Review of Exhibits*

4:30 Address: Emergencies in the Newborn Period.
John Lester Reichert, M.D., Assistant Professor of Pediatrics, Northwestern University Medical School, Chicago, Illinois.

5:00 Address: The Significance of Gross Hematuria as a Sign of Early Urinary Tract Malignancy.
Edgar Burns, M.D., Professor and Chairman of the Department of Urology, Tulane University School of Medicine; Director of the Department of Urology, Ochsner Clinic and Ochsner Foundation Hospital, New Orleans, Louisiana.

Evening Program

DINNER AND ENTERTAINMENT
GRAND BALLROOM, HOTEL STATLER

7:00 P.M.

Music:

The Lamplighters: World-famous GE Quartette.

Jane Ritter and George Tonak: Vocalist and organist, employees of Homemakers' Products Corp., N.Y.

Presidential Address: The Value of Postgraduate Education.
Alton Ochsner, M.D., New Orleans, President, Interstate Postgraduate Medical Association of North America.

Tickets:

The cost of the dinner will be $7.00 per plate, including service. Tickets will be on sale at the Registration Desk, and should be secured before Wednesday noon, October 24.

PLAN TO ATTEND THIS EVENT OF THE INTERSTATE MEETING AND ENJOY THE FELLOWSHIP OF THE MANY PHYSICIANS AND THEIR WIVES WHO WILL BE IN ATTENDANCE.

Thursday, October 25, 8:00 A.M.

8:00 Address: Hypotensive Drugs in Toxemia in Pregnancy.
Richard D. Bryant, M.D., Associate Professor of Obstetrics, University of Cincinnati College of Medicine, Cincinnati, Ohio.

8:30 Address: Treatment of Diabetes With Sulfonamides by Mouth.
Alexander Marble, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School; Physician, New England Deaconess Hospital and Joslin Clinic, Boston, Massachusetts.

9:00 Clinic: The Diagnosis and Treatment of Obscure Intra-abdominal Lesions.
Waltman Walters, M.D., Mayo Clinic; Professor of Surgery, University of Minnesota Graduate School of Medicine, Rochester, Minnesota; Past President, Interstate Postgraduate Medical Association of North America.

9:30 Address: The Cortisone Problem in General Practice as It Relates to Anesthesia and Surgery.
A. William Friend, M.D., Akron, Ohio.

10:00-11:00 *Intermission for Review of Exhibits*

11:00 Address: The Management of Angina Pectoris.
A. Carlton Ernstene, M.D., Chairman, Division of Medicine, Cleveland Clinic, Cleveland, Ohio.

11:30 Address: Newer Diagnostic Technics in the Early Detection of Glaucoma. The Schneider Foundation Eye Presentation.
Bernard Becker, M.D., Professor of Ophthalmology and Director of the Department, Washington University School of Medicine, St. Louis, Missouri.

Noon Intermission

1:30 P.M.

1:30 Address: Emergency Treatment of Severe Asthma.
Stanley F. Hampton, M.D., Assistant Professor of Clinical Medicine and Director of the Allergy Clinic, Washington University School of Medicine, St. Louis, Missouri.

2:00 Address: The Development of Cancer in Mixed Tumors of the Salivary Glands.
Edward S. Judd, M.D., Staff Surgeon, Mayo Clinic; Associate Professor of Surgery, Mayo Foundation, University of Minnesota Graduate School, Rochester, Minnesota.

2:30-3:00 *Intermission for Review of Exhibits*

3:00 Address: Drug Therapy of Tuberculosis.
Robert H. Ebert, M.D., Professor and Chairman of the Department of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

3:30 Address: The Inguinal Hernia and Undescended Testicle Problem.
H. William Clatworthy, Jr., M.D., Associate Professor of Pediatric Surgery, Ohio State University College of Medicine, Columbus, Ohio.